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TUBO-OVARIAN ABSCESS IN PREGNANCY[1]

Kianoosh Jafari Jasminka Vilovic Kos Augusta Webster and Robert C Stepto

From the Department of Obstetrics and Gynecology (Head Uwe E Freese)
Cook County Hospital Chicago Illinois USA

tract A case of tubo-ovarian abscess in a patient with n pregnancy is reported Nineteen reports of ovarian abscesses are collected from the literature analyzed The treatment is discussed

ute and chronic pelvic inflammatory disease dur pregnancy are seldom encountered Differential gnosis of pelvic pain with signs of inflammation ring pregnancy includes abortion especially minal abortion appendicitis bowel obstruction pregnancy and twisted ovarian cyst Be use of its rarity tubo-ovarian inflammatory dis- se is not often considered This diagnosis is usu y made after laparotomy

Most reported cases of pelvic inflammatory dis se have occurred in early pregnancy There has only one report of term pregnancy compli by an ovarian abscess in the English literature

The following is a case report of a patient with an ymptomatic tubo-ovarian abscess and a term egnancy

CASE REPORT

34 year-old black female gravida 3 para 2–1–0–1 at 41 eeks gestation was admitted to Obstetric Service at ook County Hospital on July 18 1974 complaining of ild labor pains

She had prenatal care at the Board of Health Clinic d had no complications She gave a history of olecystectomy three months after her second delivery 1969 At that time she was told that her tubes were bad d she would not be able to get pregnant again The atient used no contraception since 1969 and said she had ever been treated for gonorrhea or other pelvic inflam- atory diseases

At the time of hospital admission her blood pressure was 160/100 mmHg pulse 88/min, temperature 98 4°F Fetal heart tones were 142/min Uterus was term size Cervix was closed and vertex was 2 cm above the ischial spines There was moderate pitting edema of the lower extremities

As the patient was not in labor and because of hypertension it was decided to induce the labor During the course of induction a fetal distress developed and an emergency low transverse cesarean section was performed A male infant apgar 7 weighing 7 lbs 14 oz was delivered Her right tube and ovary were found to be normal In the left adnexal area there was a 12×12 cm abscess adherent to the posterior surface of the uterus lateral pelvic wall and sigmoid colon. The abscess wall was inadvertently ruptured during the process of dissection and approximately 30 cc of pus was evacuated

The patient desired sterilization but since her condition precluded hysterectomy at this time a left salpingo-oophorectomy and right Pomeroy tubal ligation was performed

Patient was given antibiotics and had an afebrile post operative course She was discharged with her baby on the 9th postoperative day both in good condition.

Histopathologic examination of the surgical specimen confirmed the diagnosis of ovarian abscess and chronic salpingitis Culture of the abscess grew Peptococcus

DISCUSSION

The etiology of pelvic inflammatory disease in preg nancy has been suggested by most authors (2 7 9 10 12 19) as follows

1) Lymphatic spread from vagina or cervix

2) Hematogenous spread from distant organs

3) Flare-up of a pre-existing infection of the tube or ovary

4) Spread by continuity from an adjacent focus such as the appendix

5) Ascending infection about the time of conception

Acute pelvic inflammatory disease during preg nancy is extremely rare Occasional reports in the literature are not well documented However

[1] Presented at the Chicago Gynecological Society Meet ng in Chicago Illinois November 1974

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Table I *Summary of documented tuboovarian abscesses in pregnancy*

TO=tuboovarian TOA=tuboovarian abscess OA=ovarian abscess TAH=total abdominal hysterectomy bilateral salpingo-oophorectomy vs =versus R=right L=left RO=right oophorectomy SO=salpingc CS=cesarean section NSVD=normal spontaneous vaginal delivery AB=abortion

Case	Length gestat	Symptoms and signs: Pain	Temperature	Peritonitis	Mass	Prior PID	Preoperative diagnosis
Aikens 1870 (7)	28 w					Yes	
Brindeau 1917 (3)	term	Yes	Yes		No		
Cron 1934 (5)	3½ mo	Yes	Low grade	No	Yes		TO mass
Mocquot 1939 (3)	2½ mo	Yes pelvic	Yes		Yes	No	
Palmer 1939 (3)	1½ mo	Yes	Yes		Yes		
Merajkar 1940 (17)	7 mo	Yes pelvic	Yes	Yes	Yes	No	Periappendicular abscess
McCall 1948 (15)	4 mo						
Cummin 1951 (6)	20 w	Yes pelvic	No	Yes	No	No	Torsion of ovarian cyst vs periappendicular abscess
Lowrie et al 1951 (14)	7 mo	Yes pelvic	Yes	Yes			Abruptio placentae
[illegible]zynski et al 1954 (4)	20 w	No	No	No	Yes	Yes	Ovarian cyst
1957 (11)	5 mo	Yes pelvic	No	No	Yes	Yes	Pelvic mass
Powell et al 1958 (18)	7 mo						
Evans 1959 (8)	25 w	Yes pelvic	Yes		No		Degenerating fibroid
Friedman 1959 (9)	6 w	Yes	Low grade	No	Yes	Yes	Ectopic pregnancy vs torsion of ovarian cyst
	28 w	Yes abdominal	No	Yes	No	No	Abruptio placentae vs torsion of ovarian cyst
Baydoun et al 1961 (?)	14 w	Yes abdominal	No	Yes	Yes	Yes	
Dudley et al 1970 (7)	1? w	Yes pelvic	Low grade	Yes	Yes	Yes	Ruptured TOA
Hunt et al 1974 (10)	25 w	Yes abdominal	No	No	No	Yes	Abruptio placentae
Jafari et al 1975	41 w	No	No	No	No	Yes	Fetal distress

…ery							
…ngs	Ruptured	Side	Opposite adnexa	Procedure	Fate of gestation	Matern death	Microorganism
…normal tube	Yes	R	Normal	Autopsy		Yes	
		R		RO	NSVD prior to laparotomy	Yes	
… size of large …ige	No	L		LSO	AB same day	No	Sterile
…purulent L …ingitis		L	Normal	LSO	Term NSVD	No	
…alpinx	No	L	Normal	LSO	AB after 36 hours	No	
…nent of ova and Fallopian tissue		R		1) abd drainage 2) abd drainage excochleation	Induced delivery prior to surgery		Streptococcus
				?	AB		
…ize of …erine …nal tube	Yes	R	Normal	RSO	Spontaneous AB after 12 hours	No	Anaerobic streptococcus
…involving …u abruptio …entae	Yes	R	Clubbed L tube normal ovary	CS RSO + cornual resection	Premature del by CS exp after 48hrs	No	E coli
…8 cm	No	R	Normal	RSO	Term NSVD supervised	No	Pneumococcus
…normal tube	No	R	Normal	RO	Term NSVD survived	No	Alpha hemolytic streptococcus
				CS SO	Neonatal death	No	
…uterus didel… pregnancy in …cornu	Yes	R	Normal	Autopsy		Yes	Anaerob strep Gram negative bacilli
…cm	No	R	Normal	RSO	AB 10 wks later	No	Streptococcus
…l cm subacute …salpingitis	No	R	Normal	RSO	Term assisted breech delivery survived	No	Sterile
…4–16 cm …hrenic abscess	Yes	R	Normal	RO drainage	AB after 9 days	No	Strep fecalis E coli
	Yes	R	Normal	TAH BSO	AB during surgery	No	Sterile
…A 10–12 cm …A 3–4 cm	No	Bil		CS subtotal hysterectomy by BSO	Premature del by CS survived	No	Proteus mirabilis
…cm adherent …ened tube	No	L	Normal	CS LSO	Postmature del by CS survived	No	Peptococcus

there are 7 cases reported in the English literature where acute salpingitis was observed at laparotomy The disease appeared usually during the 1st trimester the most advanced reported was in a patient of 24 weeks gestation (1 12 13 16 19)

Tubo ovarian and ovarian abscesses in preg nancy are also rare We have found only 19 cases described in the literature some are not described in great detail but all are documented by laparotomy These reports are summarized in Table I (2 11 14 15 17 18)

There were 6 ovarian abscesses 3 ovarian ab scesses with some tubal involvement and 10 tubo ovarian abscesses

In contrast to acute salpingitis the abscesses were rather evenly distributed throughout the pregnancy 6 were diagnosed in the 1st trimester 8 in the 2nd and 5 in the 3rd Only 2 were found at term

The symptoms of this condition are variable The most constant symptom was pain Two patients were asymptomatic One patient was operated on because of a pelvic mass (4) the other abscess was an incidental finding at the time of cesarean section Elevation of temperature was noted in about one half of the patients and it was usually of the low grade

In only one instance was the diagnosis made eoperatively (7) It was a ruptured tubo-ovarian ... s in which the mass was palpable and uldocentesis revealed pus

Cultures of the pus most frequently grew streptococcus or anaerobic streptococcus How ever 3 out of 13 cultures were sterile

There were 3 maternal deaths 2 of which oc curred prior to the antibiotic era

In the management of chronic tubo ovarian in flammatory disease with abscess formation in non pregnant patients most authors seem to agree that an aggressive approach by surgical removal of the uterus tubes and ovaries reduces the need for a second operation and the risk of other complica tions (3)

The data on chronic tubo ovarian disease in preg nancy are too limited to draw any conclusions about therapy As shown in Table I there were 9 cases of tubo-ovarian abscess in pregnancy man aged by conservative surgery i e removal of the tube and/or ovary Five of these patients aborted spontaneously and 4 pregnancies were carried to term Therefore conservative surgery in selected cases seems to be appropriate

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THE INFLUENCE OF SMOKING ON THE HAEMOSTATIC MECHANISM IN PREGNANCY

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bstract A prospective study through pregnancy is de -ribed comparing smokers with non smokers in an at ..mpt to assess possible changes in the haemostatic mech nism Various components of the coagulation and fibrin lytic enzyme systems were assayed serially up to 38 eeks of gestation Plasma fibrinogen was lower in the mokers than in the non-smokers Also plasminogen was lightly decreased and plasminogen activator activity and rum F D P increased in the former group Although ie results failed to demonstrate major disseminated itravascular coagulation in smokers the pattern of a ossible low grade syndrome emerged

.t has now been clearly established that smoking in regnancy results both in a reduced incidence of re-eclampsia and low birth weight babies (6 18 3) The mechanisms involved are unknown but ould be related to the nicotine content of the igarettes the smoking of one cigarette giving the quivalent of an intravenous dose of 1–2 μg per kg ody weight (2) Also nicotinic acid has the prop- rty of inducing intense but transient fibrinolytic ctivity when injected into normal adults (19) In ddition smoking is known to have widespread ef -cts on the haemostatic mechanim in the direction f increased coagulation (11 1)

Since abnormalities of the haemostatic mech usm have been mooted in the pathogenesis of oth pre-eclampsia and fetal growth retardation (4) was decided to compare prospectively through egnancy smokers with non smokers by assaying arious components of the coagulation and fi inolytic enzyme systems

SUBJECTS AND METHODS

wenty four normal primigravidae were selected at 12 eeks of pregnancy All had a uterine size compatible ith the period of amenorrhoea The age range was 18–25 years heights were 152 cm or over weight/height ratios were in the interquartile range (8) and there was no history of abortion hypertension or renal disease All progressed normally and delivered normal full term infants Twelve of the subjects were non smokers and 12 habitually smoked 10 or more cigarettes daily Their smoking habits were unchanged throughout the study

Blood was collected atraumatically at 12 20 25 30 34 and 38 completed weeks of gestation Plasma samples were collected into sodium citrate 3 8% solution in plastic tubes serum samples were collected into glass tubes and allowed to stand for one hour before separation Plasminogen activator assays were carried out within 30 minutes of collection and plasma and serum were stored in aliquots at −20 C for the other assays

The following parameters were measured

Fibrinogen—measured in plasma and expressed as mg/100 ml (Ratnoff & Menzie (16))

Plasminogen—measured in plasma and expressed as casein units/ml (Remmert Cohen (17))

Plasminogen Activator—measured in plasma according to the method of Nilsson & Olow (12) but converted on a log log graph to units of activity 500 minutes being assigned one unit (7)

Serum Fibrin Degradation Products (F D P)—expressed as μg/ml (Merskey et al (10) The blood had been collected into plastic tubes containing glass beads and aprotinin (Trasylol) 0 1 ml and incubated at 37°C for at least 3 hours before separation in order to inhibit in vitro fibrinolysis

Antithrombin III—measured in serum by radial immunodiffusion using Nygaard standard serum and expressed as % "normal" (Mancini et al (9))

α1 Antitrypsin and α2 Macroglobulin—measured as for Antithrombin III using Partigen Plates (Hoechst) and expressed as mg/100 ml

RESULTS (TABLE I)

Using Student s *t* test the only statistical difference recorded below the 5% level of significance was fibrinogen at 20 weeks of gestation which was lower in the smoking group ($p < 0.05$)

Table I *Components of the haemostatic mechanism in pregnancy*

Smokers compared with non smokers Means ±1 S D are recorded at each completed week of gestation

Parameter		12 weeks	20 weeks	25 weeks	30 weeks	34 weeks	38 w
Fibrinogen mg/100 ml	Non-smokers	360±95	370±60	385±66	441±82	500± 73	483±[illegible]
	Smokers	321±41	316±47	352±68	409±65	450±108	448±[illegible]
Plasminogen casein units/ml	Non smokers	4 5±0 5	4 8±0 3	4 8±0 4	4 9±0 4	4 8±0 6	4 9±[illegible]
	Smokers	4 2±0 6	4 4±0 6	4 5±0 7	4 5±0 7	4 6±0 5	4 7±[illegible]
Plasminogen activator units of activity	Non smokers	3 2±1 3	1 3±0 6	–	0 9±0 4	–	0 9 [illegible]
	Smokers	3 1±1 4	1 6±0 5	–	1 2±0 7	–	0 9±[illegible]
Serum F D P µg/ml	Non-smokers	4 4±5 0	4 6±1 7	5 1±4 8	5 8±4 0	6 7±4 1	[illegible]
	Smokers	6 5±4 4	6 4±4 2	12 4±9 5	7 6±3 5	7 7±4 7	10 7±[illegible]
Antithrombin III % normal	Non smokers	105±35	128±48	97±26	110±28	107±37	96 [illegible]
	Smokers	123±26	108±52	106±25	117±61	100±23	109±[illegible]
α1 antitrypsin mg/100 ml	Non smokers	351±116	452± 99	398±115	418± 55	416± 91	474±[illegible]
	Smokers	377±148	384±124	431±121	387±140	400±103	438±[illegible]
α2 macroglobulin mg/100 ml	Non-smokers	382±120	429±154	349±126	372±131	366±142	349±[illegible]
	Smokers	446± 87	458±120	444±128	428±172	396±108	479 [illegible]

Although no valid statistical comparison could be made between smokers and non smokers at individual gestations with regard to changes in the haemostatic mechanism various apparent patterns of difference emerged (Fig 1)

Mean fibrinogen and plasminogen levels were slightly lower throughout pregnancy and reached a lower peak in the smoking group

Fibrinolytic activity fell in the smokers to an equally low level by 38 weeks of pregnancy but at a slower rate

Serum F D P were slightly higher at each point in the smoking group

α2 macroglobulin was consistently slightly higher in the smoking group

No pattern of difference emerged for the other anti plasmin α1 antitrypsin or for antithrombin III

The patterns of difference were tested longitudinally over pregnancy for each individual parameter using Cochran s method of summation of binary probabilities (5) and the results were highly significant

Fibrinogen	$p<0.0001$
Plasminogen	$p<0.0001$
Plasminogen activator	$p<0.01$
F D P	$p<0.001$
α2 Macroglobulin	$p<0.0001$

Similarly a highly significant pattern emerged vertical testing at each gestation of the fo[ur] parameters fibrinogen plasminogen plasminog[en] activator and F D P

12 weeks	$p<0.01$
20 weeks	$p<0.0001$
25 weeks	$p<0.005$
30 weeks	$p<0.001$
34 weeks	$p<0.005$
38 weeks	$p<0.001$

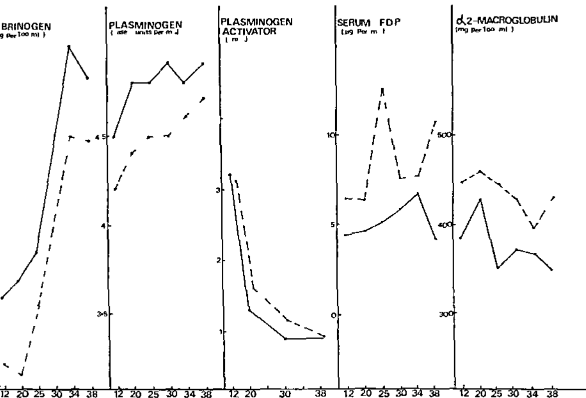
DISCUSSION

The pattern of changes observed over pregnancy [in] both groups of subjects was characteristic [of] changes in the haemostatic mechanism in normal pregnancy with an altered dynamic equilibrium be[-]tween coagulation and fibrinolysis in favour [of] systemic fibrin deposition (3 4)

This study failed to demonstrate major dissemi[-]nated intravascular coagulation in the smoking group but significant although transient phases [of] fibrin deposition associated with the smoking [of] individual cigarettes could have been overlooked

The lower fibrinogen in the smoking group m[ay] have been due to a slow intravascular coag[ulation] and fibrinolysis or to reduced synthesis of fi[-]brinogen

The significant pattern of decreased plasm[inogen]



ig 1 Components of the haemostatic mechanism in pregnancy Smokers compared with non smokers Mean levels for each parameter are depicted Units of measurement are on the vertical axis and completed weeks of gestation are along the horizontal axis Non smokers are depicted by a continuous line and smokers by a broken line

en with increased plasminogen activator activity nd increased F D P is compatible with fibrinolysis However a low grade of intravascular coagulation in association with secondary fibrinolysis ould not be confirmed in the absence of such eterminations as platelet counts and examination or fibrin monomers (14) Also using more sophisticated methods it would have been possible to ascertain whether the F D P originated from brin or fibrinogen (15)

The higher antiplasmin level in the smoking roup could have prevented further fibrinolytic tivity thus representing a possible element of hysiological compensation

A low grade intravascular coagulation in pregnancy influenced by smoking is difficult to reconcile with the coagulation theory for the pathogenesis of pre eclampsia in view of reports that smoking protects against this syndrome However such coagulopathy would be compatible with the placental insufficiency apparent in smokers (4 6 13 3)

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EFFECT OF EXOGENOUS ESTROGENS ON LH AND FSH SECRETION IN WOMEN WITH HYPOTHALAMIC AMENORRHEA

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Abstract The effects of estradiol on FSH and LH secretion in 5 women with hypothalamic amenorrhea are presented The functional capacity of the pituitary to secrete FSH and LH had been proved by testing with synthetic luteinizing hormone releasing hormone (LH RH) 100 μg i m The thyroid and adrenal functions were normal In 3 patients estrogens were low normal and in the other 2 extreme hypoestrogenism was found Twelve days after the appearance of withdrawal bleeding each patient was given 10 mg estradiol benzoat (EB) i m In 3 patients a significant increase in the LH and a slightly smaller increase in the FSH concentration were noted with an LH peak 60 to 84 hours after injection of EB The first of these 3 patients became pregnant in the second the biphasic BBT curve urine pregnanediol excretion above 2.5 mg/24 hr and the histological finding of secretory endometrium indicated that ovulation had been successfully induced while in the third patient despite a satisfactory increase in the LH and FSH concentrations ovulation could not be induced In the remaining 2 patients no increase in the LH and FSH concentrations was noted even as late as 96 hours after the injection of EB In these women bleeding began on the 18th and 22nd day of the cycle respectively when histological examination revealed proliferative endometrium The first 3 cases are classified as hypothalamic amenorrhea with dysfunction of the cyclic centre and the other 2 as hypothalamic amenorrhea with dysfunction of the tonic centre The effect of exogenous estrogens in patients with hypothalami amenorrhea depends both on the functional capacity of the hypophysis and the capacity and condition of the tonic and cyclic centres in the hypothalamus

INTRODUCTION

Hypothalamic amenorrhea denotes a condition associated with disorders of gonadotropin secretion due to abnormal functioning of the hypothalamus The gonadotropic integrity of the hypophysis can be successfuly tested by luteinizing hormone releasing hormone (LH RH) (1 2 11–13) In addition the increase in LH and FSH concentration following the administration of LH RH is influenced significantly by the level of endogenous estrogens (2 3 11)

In a normal menstrual cycle there exists a dynamic but as yet insufficiently understood mechanism regulating inter relationships on the hypothalamus–pituitary–gonadal axis in which according to Leyendecker et al (6) estrogens play an important role in the preovulatory rise of LH

The estrogen/gonadotropin ratio has been extensively studied both in the normal menstrual cycle (4 6 9 16) and in some pathological conditions (5 6 10 14 15)

The aim of this study was to ascertain whether it is possible to elicit a positive feedback effect by exogenous estrogens in women with hypothalamic amenorrhea who had been tested previously with LH RH

MATERIAL AND METHODS

Five women with secondary amenorrhea of 9 to 37 months duration were studied Total estrogens in 24 hr urine and serum LH and FSH concentrations were at a low normal level and in 2 patients (P C and G I) low gonadotropin concentrations were accompanied by extreme hypoestrogenism The thyroid and adrenal functions were normal in all cases and X ray findings did not reveal any enlargement of the sella turcica The menarche had occurred at the usual time and the secondary sexual characteristics were well developed in all cases All women had a problem of sterility All hysterosalpingographic findings were normal and the spermiograms of the husbands were also normal

The most important clinical and laboratory data of our 5 patients are presented in Table I

Table I *Laboratory and clinical data of the 5 patients*

Patient	Age	Duration of amenorrhea (months)	Before treatment TE µg/24 hr	FSH mIU/ml	LH mIU/ml	Previous treatments and results obtained with Clomiphene	Pregnancy	Proge-terone test
R K	28	9	15 6	9 5	12	2 treatments 2 ovulatory responses 2nd phase 12 days	0	+
D C	23	14	16 4	7	19 4	2 treatments 1 ovulatory response	1[b]	+
M L	32	26	17	6	14	2 treatments 1 ovulatory response	0	+
P C	24	17	9	4	5 1	2 treatments without effect	0	–
G I	26	37	7	4 2	6	3 treatments without effect	0	–

Total estrogens (TE) FSH and LH are mean values of 2 or 3 measurements
[b] In 1971 normal delivery with lactation in puerperium

The gonadotropic integrity of the pituitary was tested with synthetic LH RF (obtained from Hoechst Frankfurt Germany) administered in doses of 100 µg i m and the serum LH and FSH concentrations were determined according to the radioimmunoassay of Midgley (7 8) Two to five months after this first test the first 3 patients in Table I received 4×25 mg progesterone i m and patients P C and G I 3×1 ampoules of lutestrol (20 mg progesterone and 2 5 mg estradiol benzoate) Twelve days after the appearance of withdrawal bleeding each patient was given 10 mg estradiol benzoate (EB) i m Besides basal body temperature (BBT) serum LH and FSH concentrations were measured on the 1st 5th 10th and 11th day and between days 12 and 16 twice daily (at 7 a m and 7 p m) Pregnanediol excretion in 24 hr urine was determined on the 24th day

Endometrium samples for histological examinations ere taken on the first day of bleeding

RESULTS

Serum LH and FSH concentrations following injection of 100 µg LH RH i m are presented in Table II

The significant increase in the LH concentration and the slightly smaller increase in the FSH co[n]centration found in all patients proved the capa[ci]ty of the pituitary to synthesize and secre[te] gonadotropins

In patients P C and G I who showed an e[x]treme hypoestrogenism and a negative response t[o] Clomiphene stimulation the increase in LH a[nd] FSH concentration following LH RH was sligh[tly] smaller The LH and FSH concentrations obtain[ed] before and after administration of EB are present[ed] in Figs 1 and 2

The first 3 patients (Fig 1*a b c*) responded t[o] EB with a significant increase in LH and a sligh[tly] smaller increase in FSH concentration showing [a] LH peak 60 to 84 hr after the injection of EB

Patients D C and M L had biphasic BBT an[d] the 24 hr urine pregnanediol excretion on the 24[th] day of the cycle amounted to 3 4 and 4 6 mg re[spectively]

In both patients ovulation with a sufficient lute[al] phase was successfully induced as evidenced b[y] the consecutive pregnancy of patient M L and th[e]

Table II *Serum LH and FSH concentrations before and after administration of 100 µg LH RH i m*

Patient	LH mIU/ml Before LH RH	Minutes after LH RH 30	60	120	FSH mIU/ml Before LH RH	Minutes after LH RH 30	60	120
R K	12	39	37	29	9 5	23	25	16
D C	19 4	56	54	38	7	21	24	18
M L	14	44	45	25	6	19	21	15
P C	5 1	16	15	8	4	9	10 5	5
G I	6	21	20	9	4 2	12	14	7

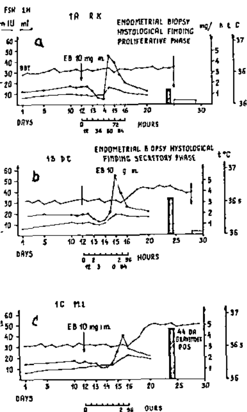


Fig 1A B C Serum FSH and LH concentration before and after EB pregnandiol in urine mg/24 h and BBT

histological finding of secretory endometrium a biphasic BBT curve and a pregnanediol excretion of above 2 5 mg/24 hr in patient D C

In patient R K ovulation could not be induced despite an adequate increase in the LH and FSH concentrations following administration of EB The BBT curve was monophasic urine pregnanediol excretion 1 4 mg/24 hr and bleeding began on the 25th day of the cycle when histological examination revealed proliferative endometrium In patients P C and G I no increase in serum LH and FSH concentrations could be noted even 96 hr following the injection of EB Their BBT curves were monophasic bleeding occurred on the 18th and 22nd day of the cycle respectively when histological examination showed proliferative endometrium

DISCUSSION AND CONCLUSION

Thanks to the use of LH RH it is now possible to differentiate between hypothalamic and pituitary amenorrhea According to Gual (2) and Espinoza Campos et al (1) hypothalamic amenorrheas can be divided into two categories

(1) Hypothalamic amenorrhea with dysfunction of the cyclic centre characterized by low gonadotropin and estrogen levels and a positive response to Clomiphene and LH RH In these patients thanks to the intact tonic centre in the hypothalamus gonadotropin synthesis and secretion are maintained to a certain degree but cyclic variations are non existent According to these criteria our first 3 patients in Table I (R K D C and M L) belong to this category of hypothalamic amenorrhea

(2) The second category consists of hypothalamic amenorrhea with dysfunction of the tonic centre In these patients besides low gonadotropin concentrations extreme hypo-estrogenism negative response to Clomiphene and low or delayed response to LH RH are found We included our patients P C and G I in the category hypothalamic amenorrhea with dysfunction of the tonic centre because in addition to low gonadotropin concentrations and extreme hypo-estrogenism they showed negative response to Clomiphene and a slow response to LH RH

The elevation of LH and FSH concentrations following administration of LH RH depends both on the functional capacity of the pituitary and the

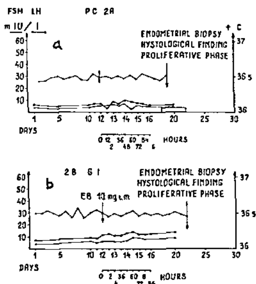


Fig 2A B Serum FSH and LH concentration before and after oestradiol benzoate (EB) pregnandiol in urine mg/24 h and basal body temperature

amount of endogenous estrogens (11) and LH RH (13)

According to Keye & Jaffe (3) estrogens elicit the midcycle gonadotropin surge acting on the level of the hypothalamus and hypophysis

In a normal cycle the preovulatory elevation of the LH concentration is preceded by an increase in the estrogen concentration which begins 120 hr before the LH peak (2) A latent period after administration of exogenous estrogens was also noted in cases of amenorrhea In oligo- and amenorrheic patients Taymor et al (14) and Thompson et al (15) found LH peaks 48 to 66 hr after injection of EB and Leyendecker et al (6) detected a significant increase in the LH concentration 2 days after i m injection of 25 mg EB and LH peaks 4 days following the injection In our 3 patients with a positive response the LH peak was observed 66 to 84 hr after injection of EB In the 2 women with dysfunction of the tonic centre in the hypothalamus elevation in the LH and FSH concentrations could not be detected even as late as 96 hr after injection of EB despite the capacity of the pituitary to synthesize and secrete gonadotropins as demonstrated by the positive response to LH RH These 2 patients with extreme hypo-estrogenism also failed to respond to Clomiphene which according to Gual (2) exerts its effects through the cyclic centre in the hypothalamus This observation supports the hypothesis of Leyendecker et al (6) who suggests that the positive feedback effect of estrogens is also exerted ia the cyclic centre It appears however that both omiphene and estrogens can elicit favorable effects only when the function of the tonic centre in the hypothalamus which maintains the synthesis and secretion of pituitary gonadotropins without cyclic variations is preserved In patients with an impaired tonic centre in the hypothalamus exogenous estrogens and Clomiphene fails to take effect In hypothalamic amenorrhea with dysfunction of the cyclic centre it is possible to elicit an increase in LH and FSH secretion by administration of exogenous estrogens and if one of the follicles is in the advanced stage of maturation rupture of the follicle and expulsion of the ovum may ensue According to Kupperman et al (5) ovulation and pregnancy can be successfully induced (our patients D C and M L) by exogenous estrogens in women with an inadequately developed follicle which before ovulation does not secrete the necessary threefold amount of estrogen i e in whom the LH peak indispensable for the rupture of the gra follicle fails to appear On the other hand an crease in the gonadotropin concentration after jection of EB with an adequate LH peak does mean that ovulation has been induced (our pa R K) Taymor et al (14) have found that ovula cannot be induced by the administration of exog ous hormones if the follicle has not reached a c tain degree of maturity despite an adequate crease in the gonadotropin concentration and LH peak like that in a normal biphasic cycle T effect of exogenous estrogens in hypothala amenorrheas does not depend on the gonadotro integrity of the pituitary alone but also on the fu tional capacity of the tonic and cyclic centres in hypothalamus In the case of an intact tonic cent exogenous estrogens may elicit a positive feedba effect while in the case of an impairment of t tonic centre exogenous estrogens in addition clinical and laboratory tests may be used f the differentiation of cases of hypothala amenorrhea into those with dysfunction of the to and those with dysfunction of the cyclic centre

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Daktar vaginalkram

Nytt antimykotikum för candida-vaginiter/vulviter



- Fungicid effekt
- Klinisk och mykologisk utlakning i cirka 90% oavsett predisponerande faktorer som diabetes, graviditet, samtidig p-piller- eller antibiotikabehandling
- Symtom som sveda och klåda forsvinner eller lindras vanligen efter 2–3 dagar
- Olja i vattenemulsion – avtvattbar, fargar ej hud eller klader

Fass-text

DAKTAR*
Vaginalkräm 2 %
Bredspektrumantimykotikum för gynekc k giskt bruk
Deklaration
100 g kräm innehåller
Miconazoli nitras 2 g
Tefose 63* Labrafil M 1944 CS* paraffinum liquidum acidum benzoicum butylhydroxaniso-lum
et aqua purificata q s
Egenskaper DAKTAR agınalkräm innehåller som aktiv substans miconazol ett imidaz lderi vat Mic nazol har såväl in vitrc som in vivo fung cid effekt mot flertalet pat gena svampar ter Såväl mykologisk som klinisk utläkning har kc nstaterats i ca 90 % av de behandlade fallen Vid behandling med DAKTAR erhålles en snabbt insättande effekt med snabb lindring av symtom som sveda klåda och fluor Behandling med DAKTAR sänker förhöjda vaginala pH värden vilket har en gynnsam effekt på den naturliga bakterieflorans tillväxt DAKTAR lämpar sig väl för behandling av symtomlös va ginit hos gravidae som profylax mot oral mykos hos det nyfödda barnet
DAKTAR resorberas i mycket ringa grad vid k kal applikation
DAKTAR har goda k smetiska egenskaper och innehåller ej lanolin eller parabener Ett fall av sensibil sering har rapporter ts Krämen färgar ej kläderna och kan a tvättas med t ål och vat ten
Klinik DAKTAR är ff kti i vid vaginiter orsakade av Cand da pp och andra svampar

Indikationer Vaginiter och vulviter orsakade av jästsvampar
Bi erkningar I sällsynta fall (mindre än 1) har lätt l kal irritation rapporterats
Dosering En fylld applikator (= 5 g kräm = 100 mg micc nazol) töms djupt i slidan vid sänggåendet Behandlingen upprepas dagligen i 14 dagar Det är viktigt för ett g tt behandlingsresultat att patienten genomför hela behandl ngen Inget uppehåll behöver göras under menstruation Vid graviditet bör appl katorn tömmas långsamt och mindre djupt i slidan Appli kator och bruksanvisning medföljer varje förpackning
Forpackningar Tub à 78 g med appl kator



För närmare information kontakta
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α 1 FETOPROTEIN IN CORD SERUM CORRELATED TO GESTATIONAL AGE

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stract Measurement of α fetoprotein by rocket im no-electrophoresis in cord serum from a consecutive ies of 472 newborn infants showed a negative correla n with gestational age The coefficient of correlation s −0 70 for girls and −0 74 for boys For a given α_1 oprotein concentration in cord blood the confidence its for prediction of gestational age for both sexes were culated to ±24 days It is concluded that determination α fetoprotein in cord serum is of limited help in the aluation of maturity

nce 1944 α_1 fetoprotein (AFP) has been known as feto specific alpha globulin (9) and for the last 10 ars as a serological marker for human hepatoma d embryonal carcinoma The concentration of is protein in maternal serum is maximal around 14th week of gestational age and thereafter de ases to reach low levels at term (2 5 6) In nor al adult sera from non pregnant subjects the iount of α_1 fetoprotein is low and not measurable immuno electrophoresis However in cases of imary liver cancer and embryonal carcinoma in ased serum α_1 fetoprotein levels reappear in ults as well as in children (1 4)

A close negative relation between the concentra n of α_1 fetoprotein in cord serum from newborn ants and gestational age has been reported re ntly (3 6 9) The purpose of the present work s to study α_1 fetoprotein in cord serum obtained m a consecutive series of newborn infants of rying gestational age

MATERIAL

samples of cord blood were collected just after deliv as a consecutive series over a 6-month period After gulation the blood samples were centrifuged and the sera were kept frozen at −18 C until determination of the α_1 fetoprotein concentration The maximal time interval between collection of samples and analysis was 3 days

With the intention of obtaining the most precise infor mation about gestational age the following criteria had to be fulfilled

Information on the exact date of the last menstrual pe riod should be available No bleeding should have oc curred during the first trimester

Pathological pregnancies with toxaemia immunisation or malformation were not included in the series Twins were not included either The birth weight of the infants was recorded by the midwife just after delivery

METHOD

α fetoprotein was determined by quantitative rocket im munoelectrophoresis as described by Laurell (7)

Apparatus Complete equipment for immuno-electro-phoresis (Dansk Laboratorieudstyr Copenhagen)

Standard α fetoprotein Standard 250 mg/l (Behrings werke Marburg)

Antibody Rabbit immunoglobulins to human α_1 feto-protein (Dakopatts Copenhagen)

Immuno-electrophoresis was carried out in a 1% agar ose gel (Litex Glostrup) in barbitone buffer pH 8 6 con taining antibody 0 7% (V/v) with 2 V/cm for 12–18 hours Standards were diluted with barbitone buffer (V/v) 1+3 1+7 1+15 and 1+31 and sera were diluted up to

Table I *The coefficients of correlation (r) between α_1 fetoprotein in cord serum gestational age and birth weight*

Correlation	♂	♀
AFP~gest age	$r=-0$ 74	$r=-0$ 70
Weight~gest age	$r=$ 0 69	$r=$ 0 56
AFP~weight	$r=-0$ 62	$r=-0$ 57

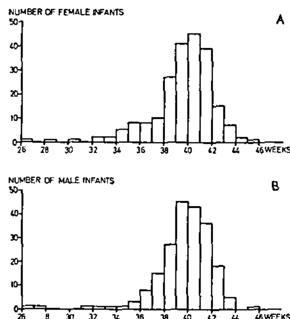


Fig 1 The cases studied grouped according to sex and gestational age

1+9 prior to analysis of 5 μl After washing the plates were dried and stained with coomassie brilliant blue By this method the lower limit of determination of α_1 fetoprotein is about 5 mg/l Day to-day variation was 6% as calculated from 10 replicate determinations on a control serum

Statistical method

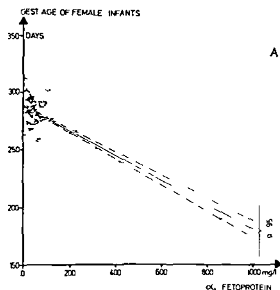
Gestational age and birth weight was correlated with α_1 fetoprotein concentration using linear regression This is permissible because for both sexes the scatter of gestational age points around the regression line is dependent of whether the gestational age is normal or very low The same argument applies to the b weight The slopes and the intercepts of the regres lines were calculated as well as the correlation coef ents the standard deviations for the position of the reg sion lines and the 95% confidence limits for estimate gestational age

RESULTS

Only 422 out of 600 cases fulfilled the above-m tioned criteria The distribution according to ge tional age for 207 girls is illustrated in fig 1A a for 215 boys in fig 1B As seen from the fig 9 girls and 19 boys were born before the 36th w of gestation The majority of the children were b at term i e with gestational age >260 days

Table I shows the correlations between the c centration of α_1 fetoprotein in cord serum the g tational age and the birth weight The coeffi ic correlation (r) for α_1 fetoprotein versus gest ag age was −0 70 and −0 74 for girls and boys resp tively This was a slightly higher degree of corr tion than for birth weight versus gestational a The correlation between α_1 fetoprotein and b weight was less pronounced r=0 57 and r=0 6 f girls and boys respectively However all corre tion coefficients are highly significant

Fig 2 shows the correlation between the concentration of α_1 fetoprotein (AFP) in mg/l a gestational age as evaluated by linear regress



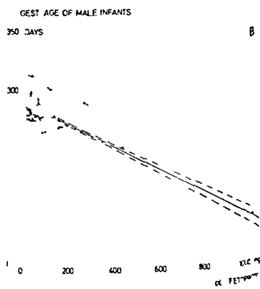


Fig 2 The correlation between α_1 fetoprotein mg/l and gestational age for female (*A*) and male infants (*B*) The dot and-dash lines indicate the uncertainty for the reg sion lines and the dotted lines the 95% confidence l

alysis For 207 girls (Fig 2 A) the following equa n was calculated Days of gestation=−0 107× P+288 The 95% confidence limits were ±23 ys

For 215 boys (Fig 2B) Days of gestation= 100×AFP+290 The 95% confidence limits re ±25 days α_1 fetoprotein=AFP in mg/l For th sexes taken together the 95% confidence its for determination of the gestational age were 4 days

For 47 preterm infants (gestational age <260 ys) we found a correlation coefficient r=−0 81 tween α_1 fetoprotein and gestational age

DISCUSSION

e results of the pre ent investigation showed that concentration of AFP in cord serum from new rn infants is correlated with gestational age al ough it is not as sound an indication of maturity stated by some authors (6 8) The calculated % confidence limit for determining gestational e by means of the α_1 fetoprotein concentration in rd serum was ±24 days This corresponds to the lue found by Bergstrand et al (3) who reported its of ±4 3 weeks In the work of Nørgaard dersen (8) the limit was ±16 days This difference ght be explained by differences in the selection d character of the cases studied In our series ants with low gestational age were less frequent represented than in the series of Nørgaard Peder n (8) According to Nørgaard Pedersen the cor lation between the concentration of α_1 fetoprotein d gestational age is better for preterm infants than r children with a gestational age over 280 days milarly we found a coefficient of correlation of 31 in preterm infants

The conclusion of our study is that determination α fetoprotein in cord serum is hardly a valuable supplement to external characteristics e g birth weight in the evaluation of maturity

However the number of preterm infants in our series is limited so that further investigations will be necessary at this point

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THE SIGNIFICANCE OF HUMAN CHORIONIC GONADOTROPIN IN BLOOD SERUM FOR THE EARLY DIAGNOSIS OF ECTOPIC PREGNANCY

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stract Determination of human chorionic gonadotropin CG) values in the serum by the radioimmunoassay hnique was performed in 23 women with suspected opic pregnancies In 16 cases the values of HCG were h and the diagnosis of ectopic pregnancy was verified laparoscopy and laparotomy In 7 cases low HCG lues were found and ectopic pregnancy was excluded e detection of HCG in the serum was found to be an ellent tool for the early diagnosis of ectopic pregnancy is helping to prevent the dangerous sequelae which fol v the late diagnosis of this condition

irly detection of an ectopic pregnancy is difficult as much as there is no simple laboratory test that ll establish the diagnosis The presence of an topic pregnancy can only be proved by surgery ie basic problem is to differentiate between ectop- pregnancy and other less dangerous situations h as persistent corpus luteum follicular cyst minent abortion and inflammatory adnexal isses

Among the laboratory methods used to diagnose opic pregnancy is the immunologic pregnancy t of the urine The sensitivity of this test is 700 /l (1 2) Jeffcoate (3) claims that this test is posi e in only 50% of all ectopic pregnancy cases Ac rding to others the accuracy of the test is between %–87 5% (4 5 6) This means that the diagnosis a very early or a pathologic pregnancy could be ssed using this method

The purpose of this study was to evaluate the lioimmunoassay technique of HCG in the serum the early diagnosis of ectopic pregnancy and s to try to eliminate the need for surgery in many pected cases

MATERIAL AND METHODS

Twenty three women were admitted to our hospital during a 1? month period (1974–5) with suspected ectopic preg nancy All (except the last 3 in the control group) under went the routine procedure of examination under anaes thesia and laparoscopy In all cases a laparotomy was per formed when the diagnosis was established On admis sion 10 ml of venous blood was drawn the serum was separated and was later sent for determination of HCG values by the double antibody radioimmunoassay tech nique (7) (The radioimmunoassay kit was supplied by Sorino-Italy)

RESULTS

Fourteen of the 23 women had ectopic pregnancies as proven by laparotomy and histology (Table I) The 9 pa tients where no ectopic pregnancies were found served as a control group (Table II)

In all cases of ectopic pregnancy HCG values in the serum were high They ranged from 182-884 mIU/ml

In the control group the range of HCG was 9 1–56 0 mIU/ml Immunologic urine tests for pregnancy were per formed in only 9 out of the 14 cases with the ectopic preg nancy Five gave negative and 4 gave positive results In the control group all cases showed negative results

DISCUSSION

An early diagnostic test for ectopic pregnancy would help to decrease the morbidity and mortality rate In many cases it could change the prognosis for future pregnancies

The urine immunological pregnancy test is not satisfactory for early diagnosis of ectopic preg nancy because of its low limit of sensitivity A nega tive result does not exclude trophoblastic activ ity (8)

Table I *Values of HCG in blood serum in cases of ectopic pregnancy*

Patient No	Age	Week of pregnancy	Laparoscopy	Laparotomy	HCG (mIU/ml)	HIT
1	30	8	+	+	884	Negative
2	30	7	+	+	611	–
3	25	7	+	+	442	Negative
4	22	7	+	+	806	–
5	24	7	+	+	182	–
6	31	9	+	+	80 6[b]	Negative
7	26	8	+	+	598	Positive
8	28	6	+	+	299	Positive
9	24	8	+	+	702	Positive
10	35	6	+	+	728	–
11	24	6	+	+	364	Positive
12	32	6	+	+	552	Negative
13	34	8	+	+	325	–
14	24	6	+	+	858	Negative

Haemagglutination Inhibition Test
[b] In this case the blood was taken two days after the operation

Barjaktarovic (9) in 1934 showed that the placenta in cases of ectopic pregnancy secretes less HCG than a placenta of a normal intrauterine pregnancy of the same gestational age This was later confirmed by others (10 11)

The radioimmunoassay of HCG in the serum offers a much more sensitive test for measuring trophoblastic hormones in the serum than the urine test

In all 14 cases where a high level of HCG was found an ectopic pregnancy was proved by laparoscopy and laparotomy In 6 of the patients where HCG levels were low laparoscopy excluded the ibility of an ectopic pregnancy In the last 3 low values of HCG were measured and laparoscopy was not performed These patients were carefully observed till normal periods resumed a few weeks later

Early diagnosis of ectopic pregnancy may have great significance for the reproductive future o woman It would enable an early surgical proce which might prevent tubal rupture with its as ated haemorrhage and shock A conservative t plasty sometimes may be the procedure of ch

For the non pregnant woman having sympt similar to an ectopic pregnancy the low HCG le determined using the radioimmunoassay test w avoid the need for general anaesthesia the op tive procedure of laparoscopy and curettage save hospital time

Luteinizing hormone (LH) and HCG have munologic cross reaction in this method The ues of HCG+LH measured in all 14 cases of ec ic pregnancy were higher than 150 mIU/ml In non pregnant woman the highest value was mIU/ml We feel that a value of 150 mIU/ml serve as the diagnostic limit between a pregnant non pregnant woman However it is possible

Table II *Values of HCG in blood serum in cases without ectopic pregnancy*

Patient No	Age	Laparoscopy	Laparotomy	HCG (mIU/ml)	HIT
1	33	+	–	9 1	Negative
2	24	+	–	22 1	Negative
3	27	+	–	7 0	Negative
4	38	+	–	22 0	Negative
5	32	+	–	13 0	Negative
6	30	+	–	37 5	Negative
7	25	–	–	43 0	Negative
8	25	–	–	49 0	Negative
9	30	–	–	56 0	Negative

very rare cases one may find high levels of LH ing the mid cycle surge in normal menstruating men

This problem can be resolved by using a test ich differentiates between HCG and LH The erentiation is performed by measuring the HCG ubunit Although this test is somewhat longer it vides the physician with a more positive diag tic procedure

n conclusion it seems that the measurement of G in the serum by the radioimmunoassay tech que is an important tool in the early diagnosis of opic pregnancy

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PNEUMOPERITONEUM WITHOUT CLINICAL PERITONITIS DUE TO BILATERAL PYOSALPINX

Odd Søreide Willy Haukeland and Tormod Bjerkeset

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stract A case of pneumoperitoneum without clinical ıtonitis due to bilateral pyosalpinx is presented This ıcal condition has in the literature been called ontaneous or idiopathic pneumoperitoneum and at ve treatmen n such cases has been advocate rathd

were experienced On admission it was noted that her abdomen was moderately distended but no signs of peritonitis Temperature 38 0°C Hbg 14 3 g WBC 23 600 per mm³ Sedimentation rate 48 mm/hour Blood glucose 3 mg% The patient s diabetes mellitu vas insul

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stract A case of pneumoperitoneum without clinical ritonitis due to bilateral pyosalpinx is presented This nical condition has in the literature been called pontaneous or idiopathic pneumoperitoneum and nservative treatment in such cases has been advocated shown in our case severe intraperitoneal pathology ay exist and we therefore advocate early explorative parotomy in all patients with pneumoperitoneum with- it peritonitis

he term pneumoperitoneum is used to describe the esence of free gas in the peritoneal cavity In ost patients pneumoperitoneum is considered as idence of an abdominal catastrophe and is usually companied by signs of peritoneal irritation or ritonitis (6) In such cases immediate surgical in- rvention is mandatory

An etiological classification of pneumoperito- um has been presented by Loughead (10) ig 1 shows a modification of his classification stem with reference to the actual literature

Pneumoperitoneum due to intraperitoneal infec on caused by gas producing organisms of non ostridial origin has been reported by other authors 14) Recently one case was encountered with neumoperitoneum without clinical peritonitis At irgery bilateral pyosalpinx was found No similar ises of this nature were found in the literature As new cause is added to the list for differential agnosis of pneumoperitoneum it is felt that a port is indicated

CASE REPORT

N a woman aged 73 was admitted to the medical partment Sept 18th 1973 with the diagnosis of diabetic ecoma She had previously been healthy except the last 4 months when polydipsia polyphagia and polyuria were experienced On admission it was noted that her abdomen was moderately distended but no signs of peritonitis Temperature 38 0°C Hbg 14 3 g% WBC 23 600 per mm³ Sedimentation rate 48 mm/hour Blood glucose 344 mg% The patient s diabetes mellitus was treated with insulin

During her stay in the medical department it was noted that the abdominal distension increased The possibility of ileus/subileus was discussed and an X ray of the colon was performed Sept 27 During this examination which showed displacement of the rectum possibly due to a pelvic tumour massive pneumoperitoneum was found (Fig 2)

A careful physical examination was again performed The patient had no abdominal pain or no signs of peritonitis A check plain X ray of her abdomen disclosed increasing pneumoperitoneum and the patient was admit ted to the surgical department Physical examination showed an afebrile woman The abdomen was distended and there were normal bowel sounds No abdominal tumor could be found Hgb 14 2 g% WBC 13 800 per mm³ Sedimentation rate 31 mm/hour

On Oct 8 laparotomy revealed bilateral pyosalpinx and a salpingo-oophorectomy was performed Bac teriological study of the pus showed E coli Proteus mirabilis and non-hemolytic streptococcus No anaerobic bacteria could be demonstrated Postoperative plain X ray of the abdomen showed disappearance of the pneumoperitoneum

DISCUSSION

Pneumoperitoneum without clinical peritonitis is a rare experience in surgical practice This clinical condition has in the literature been called spontane ous or idiopathic pneumoperitoneum (1 7 10 16) and many authors advocate conservative manage ment and close observation in asymptomatic pneumoperitoneum of undertermined origin (3 13 19)

As demonstrated in our case intra abdominal

ETIOLOGY OF PNEUMOPERITONEUM				LITTERATURE
MECH N CAL	DIAGNOST C AND THERAPEUTIC PROCEDURES		POSTOPERATIVE	Br J Rad ol 17 119, 1944
			THERAPEUTIC AND DIAGNOSTIC	Coc h V S hinz Glasser and V hl nger Roentgendiagnostik Georg Th em Ve lag Berl 1944
			LAP ROCENTESIS	
			FOLLOWING TEST FOR PATENCY OF FALLOPIAN TUBES	Ar h urg
	WOUNDS	EXTERNAL	ABDOM NAL WALL INCLUDING PERITONEUM	B J Rad l 18 390 19 5
		INTERNAL	PE FORATION BY RECTAL THERMOMETERS ENEMA TIP ETC	Gabr W Surge p F fth Ed Sa l Ltd London 19
			AIR INSUFFLATION GASTROSCOPE	Gas oe terolog 6 2 8 1 5
			AIR INSUFFLATION PROTOSCOPE / SIGMOIDOSCOPE	Ar h S rg 42 850 1941
			AIR CONTRAST BARIUM ENEMA	Gas oen log 15 458 19 0
			VAGINAL DOUCHING	A h S rg 78 500 1959
			PNEUMOTHORAX ACCIDENTAL PUNCTURE	South Med J 39 620 1946
			PNEUMOTHORAX THROUGH HIATAL OPENI GS FISTULA	Go oe log 66
SPONTANEOUS			PERFORATION OF VISCUS	Amer J Surg 113 567 196
			DUE TO UN NOWN CAUSE	Am J Surg 101, 232 1 1
			STERO D PERFORAT ON OF THE COLON	A h Surg 100 61 1970
FALSE			HEPATIC FLEXURE OF COLON BETWEEN LIVER AND DIAPHR GM (CHILIADITIS SYNDROM)	F leman Dahl J Roentgen amina on A te bdom nal
			TRANSPOSITION OF VISCERA WITH STOMACH AIR	D seases p 59 Th rd Ed on
			BUBBLE UNDER RIGHT D APHRAGM	Charl C Thomas 1974
			SUBPULMONARY AIR	
OTHERS			AEROPHAGIA	Cl l nd Cli Quar 32 149 96
			PNEUMATOSIS CYSTOIDES INTESTINALIS	J T auma 14 435 974
			ERRONEOUSLY PLACED INHALATION TUBES DURING ANESTHESIA PROCEDURES	Am S g on 22 323 19 6

Fig 1 Etiological classification of pneumoperitoneum with reference to literature

pathology may exist without clinical symptoms in patients where pneumoperitoneum is found Peritonitis with pneumoperitoneum caused by bacteria of non clostridial origin has been demonstrated (14) The gas in these cases has been cau by Gram negative intestinal bacteria of which coli is well known to produce gas due to fermen tion of carbohydrates (2 14)

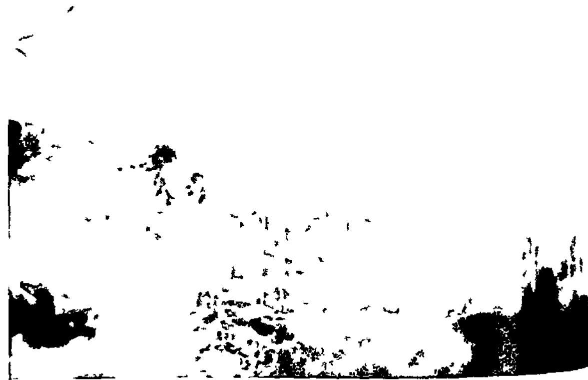


Fig 2 Plain abdominal X ray demonstrating free intraperitoneal gas

he bacteriology of intra peritoneal infections recently been studied (18) It was shown that ures commonly contained many different teria Anaerobic bacteria were isolated most uently Many of these anaerobic bacteria as l as facultative anaerobic micro-organisms may gas producing (2 8)

pontaneous or idiopathic pneumoperitoneum is cussed in detail by other authors (3 5 12) We eve that this term is perhaps a misnomer Many hors use the term in cases where clear intra ominal pathology is demonstrated (7 9 11) The rds spontaneous or idiopathic in these cases not descriptive but are used to stress the fact t no signs of intra abdominal pathology could be nonstrated prior to operation Only few cases of opathic pneumoperitoneum are found in modern rature (13 19) The important fact is that umoperitoneum is a sign of grave intra dominal pathology as in steroid perforations of colon where the clinical signs are vague (17) ncerning treatment of pneumoperitoneum with t peritonitis we completely disagree with authors o advocate conservative management We feel t excluding intraperitoneal pathology in a patient th pneumoperitoneum without clinical symp- ms is difficult A high grade of suspicion is man tory in such cases and an explorative laparotomy ould be performed in all patients

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STUDIES IN CHOLESTASIS OF PREGNANCY

VI Fatty Acid Composition of Glycero-phospholipids before and after Delivery

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stract Eight pregnant women complaining of ıeralized pruritus with lipoprotein X (LP X) in their um and diagnosed as cases of cholestasis of pregnancy P)—were studied during pregnancy and after delivery n women with uncomplicated normal pregnancy served controls LP X liver function tests and relative fatty d composition of serum lecithin (determined by gas uid chromatography GLC) were followed The fatty d composition in liver and serum lecithin is determined the synthesis pathways of lecithin in the liver The ter and quantitatively dominating cytidine-diphosphate lyceride pathway pathway I causes the appearance of ithin with palmitic acid (16 0) in 1 position and oleic 1) or linoleic (18 2) acid in 2 position while pathway with methylation of phosphatidyl-ethanolamine (cepha) preferentially causes the appearance of lecithin with aric acid (18 0) in 1 position and arachidonic acid 4) in 2 position Pathway I is enhanced by oestrogenic 1 pathway II by cholestatic influence During preg ıcy women with CP were characterized in their serum ithin fatty acid composition by a high palmitic (16 0) 1 a high oleic (18 1) acid content in agreement with her studies After delivery in women with prior CP a rease in palmitic (16 0) and linoleic (18 2) acids and increase in stearic (18 0) acid was interpreted as de ased influence on the major lecithin synthesis pathway nd an enhancement of pathway II In addition after ivery in the lactating mother serum lecithin fatty acid nposition data revealed an essential fatty acid (EFA) onsumption It was earlier shown that women with vious CP (when studied 8-21 months after delivery) l as judged from their serum lecithin fatty acid composi ı a basic metabolic defect expressing presumably estrogen enhanced pathway II of liver lecithin synth

In the present study soon after delivery (on day 4-8) men with prior CP showed however less pathway II uence than women with a prior normal pregnancy s was interpreted as a persistence of the cholestatic uence on liver lecithin synthesis pathways at this short e after delivery Serum lecithin fatty acid composition ears to be a sensitive variable for the evaluation of abolic influences in the liver

Lipid metabolism is altered in pregnant women with cholestasis i e cholestasis of pregnancy (CP) as compared to normal pregnant women (6 8 13) The cholestatic pregnancy as other cholestatic condi tions is accompanied by the occurrence in serum of an abnormal lipoprotein lipoprotein X (LP X) that might at least partially explain the increased se rum lipid levels The serum concentrations of cholesterol triglycerides and phospholipids are higher in CP and reach a maximum level just before delivery (8 13) After delivery all symptoms and signs of CP subside rapidly and laboratory data usually return to normal within two or three weeks after delivery (7)

The aim of the present study was to follow the disappearance of LP X and the characteristic fatty acid pattern of serum lecithin before and a few days after delivery in women with CP

MATERIALS AND METHODS

Clinical series Eight women (mean age 25 7 range 21-29 years) with generalized pruritus but with otherwise un- complicated pregnancy were studied Blood samples were drawn during pregnancy (weeks of gestation mean 39 9 range 39-41) and on day 4 to day 8 after delivery

Control series Ten women (mean age 24 2 range 20-28 years) without symptoms or signs of pruritus and with otherwise normal pregnancy served as control series Blood samples were drawn during pregnancy (weeks of gestation mean 40 2 range 39-40) and on day 4 to day 8 after delivery

Blood samples were drawn in the fasting state in the morning Blood was allowed to clot for 30 minutes at room temperature and was then centrifuged at 2500 r p m for 20 minutes Serum specimens for gasliquid chro-

matography (GLC) analyses were immediately frozen and stored at −20°C in glass tubes with teflon screw caps

Liver function test, total serum bilirubin (normal<1 2 mg/100 ml) Alkaline phosphatase (normal<260 units/l) SGOT (ASAT) (normal<17 units/l) and SGPT (ALAT) (normal<17 units/l) were determined at the Laboratory of Clinical Chemistry according to standard methods

Lipoprotein X (LP X) Semi-quantification of LP X was performed by double immunodiffusion in 1% agar gel employing barbital buffer pH 8 6 ionic strength 0 05 Rabbit serum containing antibodies to human LP X was obtained through the courtesy of Dr D Seidel Heidelberg West-Germany All plates were kept in a moist chamber at room temperature and the immunoprecipitin lines were visually evaluated For details in methods cf (7)

Gas liquid chromatography (GLC) procedure Preparation of lipid extracts separation of lipids by thin-layer chromatography on Silica gel and isolation of lecithin and phosphoglyceride spots and preparation of fatty acid methyl esters were performed as described earlier (6) GLC of methyl esters measurement of serum lecithin and lecithin fatty acids and conversion from weight per cent to mole per cent have been described in an earlier publication (6)

Statistical methods Conventional methods were used for the calculation of means standard deviations and standard error of means Student s t test was used to study differences between groups Values of $p \geq 0$ 05 were considered statistically significant (2)

RESULTS

nical data In the series of women with CP no trical complications occurred during delivery ntal and infant birth weights were within ex cted limits After delivery day 4–day 8 at the time of blood sampling none of the women re vealed pruritus and all were lactating Identical data were true for the control series

Liver function tests After delivery at day 4–day 8 liver function tests were within normal limits in the series of women with CP Mean SGOT and SGPT were reduced as compared to during preg nancy

Lipoprotein X (LP X) During pregnancy all women with CP revealed LP X in serum After delivery already at the first examination on day 4–day 8 LP X had disappeared in all women with prior CP

Fatty acid composition of serum glycero-phospholipids In women with CP the fatty acid composition of glycero phospholipids (GPL) showed identical changes with those of lecithin (PC)

Table I *Relative composition of major fa… of serum lecithin and mean differences (Δ) in … en with cholestasis of pregnancy (n=8 wee… gestation mean 39 9 range 39–41) and in … women 4–8 days after delivery*

Figures are given in mole per cent of methyl este… level 0 01 level

	Cholestasis of pregnancy			
	During pregnancy ($x \pm$S E M)	4–8 days after delivery ($x \pm$S E M)	Non-preg vs pregr Δ	t
16 0	35 0±0 72	33 0±0 73	−.0	
18 0	10 0±0 94	11 9±0 50	+1 9	
18 1 (*n* 9)	13 9±0 56	15 1±0.51	+1 ?	
18 2 (*n*-6)	27 2±0 98	24 6±1 14	−? 6	
20 3 (*n*-6)	3 2±0 16	3 4±0 18	+0 ?	
20 4 (*n*-6)	5 2±0 36	5 8±0 37	+0 6	
22 6 (*n* 3)	2 7±0 31	2 6±0 38	−0 1	
18–22 (*n*-6)	37 8±0 62	34 2±0 75	−3 6	
Total serum lecithin (mg/100 ml)	258±14 5	194±16 8	−64	

Fatty acid composition of serum lecithin (PC)

I *After delivery as compared to during pre…* (*week 39–41*) In the series of women with CP … ble I) the mean fatty acid composition showe…

Table II *Relative composition of major f… of serum lecithin and mean differences (Δ) … mal pregnant women (n=10 weeks of ges… mean 40.2 range 39–41) and in same wome… days after delivery*

Figures are given in mole per cent of methyl este… level * 0 01 level

	Normal pregnancy			
	During pregnancy ($x \pm$S E M)	4–8 days after delivery ($x \pm$S E M)	Non-preg vs preg Δ	t
16 0	35 1±0.53	32 2±0 4	−.9	
18 0	10 3±0 24	11 0±0 29	+0 7	
18 1 (*n* 9)	12 3±0 28	13 6±0 63	+1.3	
18 2 (*n*-6)	22 6±0 72	24 1±0 75	+1.5	
20 3 (*n*-6)	3 5±0 13	3 1±0 18	−0 4	
20 4 (*n*-6)	6 9±0 61	7 8±0 45	+0 9	
22 6 (*n* 3)	5 2±0 35	4 3±0 28	−0 9	
18–22 (*n*-6)	33 8±0 85	35 7±0 60	+ 1	
Total serum lecithin (mg/100 ml)	245±39 0	216±9 4	−?9	

e III *Mean differences (Δ) (mole per cent) in position of major fatty acids of serum lecithin omen with cholestasis of pregnancy (CP) (n=8) compared to normal pregnant women (n=10) ng pregnancy (weeks of gestation mean 40) and days after delivery*

level * 0 01 level 0 001 level

	During pregnancy CP vs normal		4–8 days after delivery CP vs normal	
	Δ	P	Δ	P
	−0 1	–	+0 8	–
	−0 3	–	+0 9	–
(n 9)	+1 6		+1 5	–
(n-6)	+4 6		+0 5	–
(n-6)	−0 3	–	+0 3	–
(n-6)	−1 7		−2 0	
(n 3)	−2 5		−1 7	
2 (n-6)	+4 0		−1 5	–
l serum lecithin /100 ml)	+13	–	−2?	–

owing changes after delivery Palmitic acid 0) ($p<0$ 05) linoleic acid (18 2) ($p<0$ 01) and of n-6 ($p<0$ 01) were lower and stearic acid 0) ($p<0$ 05) and oleic acid (18 1) ($p<0$ 05) e higher after delivery Also calculated con tration of serum lecithin was lower ($p<0$ 01)

n the *control series* (Table II) the mean changes atty acid composition of lecithin after delivery e characterized by lower palmitic acid (16 0) 0 01) and 22 6 ($p<0$ 05) and higher stearic acid 0) ($p<0$ 05)

CP as compared to normal pregnancy during nancy (Table III) The mean fatty acid com ition of serum lecithin in women with CP was racterized by a lower content of arachidonic d (20 4) ($p<0$ 05) and of 22 6 ($p<0$ 001) and a ier content of oleic acid (18 1) ($p<0$ 5) of leic acid (18 2) ($p<0$ 01) and of sum of n-6 0 01)

I *CP as compared to normal pregnancy after very* (Table III) The mean fatty acid composi of serum lecithin in women with prior CP was er in arachidonic acid (20 4) ($p<0$ 01) and in 6 ($p<0$ 001) than in the control series

DISCUSSION

man lecithin composes 69% of serum phos olipids Lecithin transported by serum lipo-proteins originates preferentially in the liver and is there synthesized along different intracellular pathways The faster and quantitatively most important pathway is cytidine-diphosphatecholine diglyceride pathway (pathway I) which prefer ably gives palmitic acid (16 0) in 1 position and linoleic (18 2) or oleic (18 1) acid in 2 position This pathway for the synthesis of lecithin in the liver is stimulated by the presence of bile acids (3) The second important pathway (pathway II) cytidine-diphosphate ethanolamine methylation pathway causes the appearance of lecithin contain ing stearic acid (18 0) in 1 position and arachidonic acid (20 4) as well as other poly unsaturated fatty acids of longer chain length and greater unsatura tion e g 22 6 in 2 position Pathway II is more active in the female and during the influence of estrogens (1 4)

After delivery as compared to during pregnancy women with cholestasis of pregnancy (CP) revealed two patterns of changes in their relative fatty acid composition of serum lecithin Firstly evidence for a decrease in pathway I simultaneously with an increase in pathway II characterized by a decrease in palmitic and linoleic acids and an increase in stearic acid Secondly the fatty acid changes may express a relative deficiency of essential fatty acids (EFA) with a decrease in sum of n 6 with a com pensatory increase in non essential oleic acid

Also in normal pregnancy changes after delivery in serum lecithin fatty acid composition indicated a decrease in pathway I and simultaneously an in crease in pathway II as judged from inverse varia tions in palmitic and stearic acids This in turn would suggest that the normal pregnancy as such is cholestatic (12) An alternate explanation would be that the characteristically high serum lecithin in the pregnant state would require an increased leci thin synthesis mediated presumably by the major pathway I (11)

In an earlier study (10) women with previous CP (studied 8–21 months after delivery) revealed as judged by their serum lecithin fatty acid composi tion a basic metabolic defect This basic defect was characterized by increased stearic and ara chidonic acids due possibly to an estrogen enhanced pathway II In the present study after delivery (day 4–day 8) women with a prior CP showed a lower content of arachidonic acid and 22 6 than wom en with a prior normal pregnancy This might in dicate that the change after delivery tow ds an

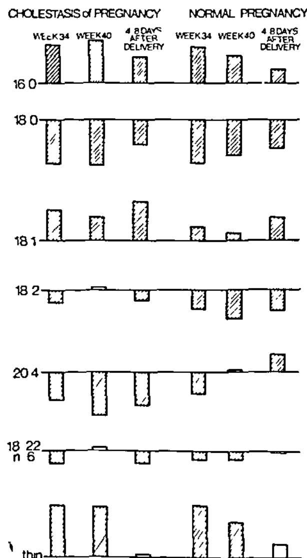


Fig 1 Changes in relative fatty acid composition of serum lecithin Changes (expressed as per cent) between non pregnant state and gestational week 34 and 40 and 4–8 days after delivery in women with cholestasis of preg nancy (CP) and in normal pregnant women Values for the non pregnant state (from series of previous CP' 8–21 months after delivery (10)) and of normal non pregnant women (11) respectively Shadowed areas indi cate significant changes

estrogenic influence on pathway II was retarded in women with prior CP by a remaining influence from the cholestasis The present method for evaluating metabolic influences in the liver by changes in serum lecithin fatty acid composition appears from these data to be more sensitive than those commonly used (i e liver function tests and LP X identification) The disappearance of cholestasis after delivery apparent from the serum lecithin fatty acid composition data (Fig 1 the reverse pattern to that seen in the develop of CP Through the steps of pruritus gravid (PG) of short and long duration into hepato pregnancy (HP) serum lecithin fatty acid comp tion revealed initially an enhanced pathway II t ing into a cholestatic pathway I influence (5).

A lower level of essential fatty acids (EFA) an increase in oleic acid after delivery in wo with prior CP is intriguing (Fig 1) It cou expected that women with CP might suffer fr latent malabsorption of EFA due to a reduced cess of bile acids in the intestine However present study reveals no obvious lack of EFA during pregnancy Breast milk from the moth a high content of linoleic acid (3 5% of t calories) to make up for low EFA in the new baby (9) Thus after delivery the milk produ would be expected to drain EFA from mother a lactating mother with a 3 kg baby w lose >1 g as linoleic acid per day In the p ence of a latent EFA deficiency during preg a true deficiency in EFA could possibly be app during lactation Because of this EFA defici should be looked for in mother and child after d ery particularly after a cholestatic pregnancy

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ULTRASONIC ASSESSMENT OF FETAL GROWTH

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bstract Consecutıve ultrasonıc measurement of fetal ıparıetal dıameter (B P D) and fetal chest area was car ed out ın 152 normal and 59 complıcated pregnancıes etween 25 and 40 weeks of gestatıon In normal preg ancy the mean fetal head area (B P D ²) varıed from 5 0 cm² at 25 weeks to 98 0 cm² at 40 weeks The mean hest area varıed from 31 3 cm² at 25 weeks to 94 3 cm² at 1 weeks A normal curve of the head to-chest relatıon 'as constructed In the group of complıcated pregnancıes vo types of fetal growth retardatıon could be recognızed 'he fırst type was characterızed by a normal head to-hest relatıonshıp (symmetrıc type) the second type was ıaracterızed by an abnormal head to-chest relatıonshıp ısymmetrıc type relatıvely large head area) Durıng fetal rowth acceleratıon head to-chest relatıonshıp was ab ormal (relatıvely large chest area)

INTRODUCTION

ccordıng to Campbell (1 2) measurement of the ıparıetal dıameter (B P D) ıs the most precıse fetal easurement that can be obtaıned antenatally In cent years however ıncreasıng attentıon has been ıd to ultrasonıc measurements of the fetal chest 0 11 17) and upper abdomınal regıon (4 5) ın latıon to fetal growth retardatıon and accelera ɔn

The objectıve of the present study was to assess hether antenatal measurement of fetal chest sıze ould provıde ınformatıon complementary to that cephalometry

The results are presented ın two parts In the fırst ırt fetal head and chest sıze ın relatıon to fetal aturıty durıng normal pregnancy ıs establıshed In e second part the sıgnıfıcance of serıal measure ents of fetal head and chest sıze durıng complı ıted pregnancy ıs demonstrated

METHODS

l Ultrasonıc measurements were performed on the asonograph 4102 Fetal head sıze was assessed by means of measurement of the bıparıetal dıameter (B P D ın mm) accordıng to Campbell's method (1) For the measurement of the fetal B P D a sound velocıty of 160(m per second was used Accordıng to Wıllocks (?0) thı: velocıty ıs the optımum fıgure for assessıng the true heac sıze As sound velocıty ın soft tıssues ıs about 1 540 m per second thıs velocıty was applıed for our fetal ches sıze measurements Fırst a longıtudınal B mode Ultrasonogram of a sagıttal sectıon of the foetus was obtaıned The fetal spıne was then located Subsequently the transverse sectıon at rıght angles to the fetal spıne ımmedıately caudal to the fetal heart pulsatıons was obtaıned and could be demonstrated on a transverse B mode Ultrasonogram (Fıg 1) At thıs level a sectıon of the fetal lıver can always be vısualızed A polaroıd photo-graph was made and measurement of the fetal chest area (ın cm²) at thıs level was carrıed out by means of a planımeter

In 3 patıents ten ultrasonıc B P D —and ın another 3 patıents nıne ultrasonıc chest recordıngs were performed wıthın 24 hours on each foetus (Table I) In about 95% o the cases an ındıvıdual measurement of the B P D fel wıthın ±1 3 mm (2×S D) and of the fetal chest area



Fıg 1 Ultrasonogram showıng transverse sectıon of the fetal chest area ımmedıately caudal to the fetal heart pul satıons *S*=fetal spıne *A*=aorta *L*=fetal lıver

Table I *Evaluation of the reproducibility of fetal B P D and chest area measurement*

$\bar{x}$ = mean value S D = standard deviation

Case no	$\bar{x}$	S D	n	
Fetal biparietal diameter (B P D in mm)				
A	90 0	0 37	10	
B	78 3	0 94	10	Mean S D =
C	99 9	0 66	10	0 70
Fetal chest area (cm²)				
A	63 91	0 925	9	
B	33 98	0 708	9	Mean S D =
C	34 30	0 875	9	0 841

within ±1 7 cm² (2×S D) of the expected mean indicating a high degree of reproducibility

Patients

Two hundred and eleven patients were studied In 152 *cases pregnancy was normal and in 59 cases complicated* Each patient was certain of the date of her last menstrual period Pregnancy was defined as normal when no antenatal complications occurred and fetal birth weight varied between the 10th–90th percentile according to the tables of Kloosterman (14) corrections being made for maternal parity and fetal sex *Consecutive measurement* of the fetal B P D and chest area was performed once in each patient of the normal group and once or more in patients of the complicated group

RESULTS

pregnancy

In order to be able to compare fetal head area measurements with fetal chest area measurements the B P D ² instead of the B P D was taken into *account*

Fetal head and chest area measurements were plotted against gestational age (Figs 2 and 3) The mean head area varied from 45 0 cm² at 25 weeks to 98 0 cm² at 40 weeks gestation After 37 weeks *there appears to be a decrease in the growth rate of* the head area The mean chest area varied from 31 3 cm² at 25 weeks to 94 3 cm² at 41 weeks Mean values and standard deviations of head and chest area are given in Table II In Fig 4 fetal head area values are plotted against fetal chest area values in order to evaluate normal head-to-chest relation between 25 and 41 weeks gestation

Complicated pregnancy

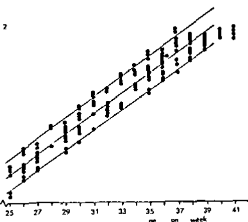
Fetal head and chest area values are evaluated against fetal birth weight This was classified according to the tables of Kloosterman (14) ... tions being made for maternal parity and fe... Fetal B P D measurements which were perf... before 25 weeks of gestation were initially plo... Campbell's B P D *growth curve (3)* Whe... than one ultrasonic measurement of the fetal B... and chest area was performed only the most re... measurement was taken into account The ... between this measurement and actual delivery ... *ied from one day to 5 weeks with a mean durat...* 24 days

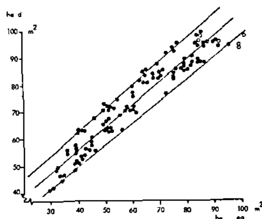
In 18 cases fetal birth weight was situat... tween the 10th–90th percentile (normal) in 9... below the 10th percentile (small-for-dates) and ... *cases above the 90th percentile (large-for-da...* weight of gestation Details are given in Tab...

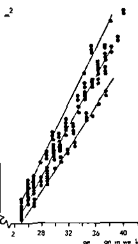
In the normal weight group both fetal head ... chest area were within the normal range in the ... jority of the cases In 3 cases however head ... *was within and chest area just below the nor...* range In the small-for-dates group both fetal h... and chest area were within the normal ra... one case In the remaining 28 cases 2 type... growth retardation could be distinguished The ... *type (n = 7)* was characterized by a small head ... chest area with a normal head-to-chest rel...

Table II *Mean fetal head area and chest ... values ($\bar{x}$) with standard deviations (S D) be... 25 and 41 weeks of menstrual age in norm... nancy*

Gestational age (wks)	No of cases	Mean head area (= B P D² in cm²)		Mean chest area (cm²)	
		$\bar{x}$	S D	$\bar{x}$	S...
25	8	45 0	3 9	31.3	
26	10	51 6	3 7	37 7	[illegible]
27	10	57 2	4.3	37 8	[illegible]
28	6	60 8	3 4	44.3	[illegible]
29	10	61 6	3 4	45.3	[illegible]
30	10	65 9	3 8	52..	[illegible]
31	10	71 1	4.3	51 9	[illegible]
32	9	73 6	4 .	57 4	[illegible]
33	7	77 4	5.5	58..	[illegible]
34	7	82 1	3.3	68 4	
35	12	83 3	6 3	7 6	
36	13	86 0	3 3	77 6	
37	10	92 8	5 1	80 5	[illegible]
38	11	92 6	3 7	81 7	[illegible]
39	8	94 2	7 4	87 4	[illegible]
40	5	98 0	7 3	90.3	
41	6	96 0	3 6	94.3	







Figs 2 3 and 4 The 10th 50th and 90th percentile of the normal curve for fetal head area (Fig 2) fetal chest area (Fig 3) and fetal head to chest relationship (Fig 4) between 25 and 39 weeks gestation The open circles in Fig 4 represent the head and chest area values at 40 and 41 weeks of gestation

licating a symmetric growth retardation This be of growth retardation usually started between 22nd and 28th week of gestation

The second type (n=21) showed a normal to nall fetal head area and small chest area with an normal head to chest relationship indicating an ymmetrical growth retardation This type of owth retardation started during the 3rd trimester all cases Figs 5 and 6 show a longitudinal low up of fetal head and chest area in a patient om the first and second sub group respectively

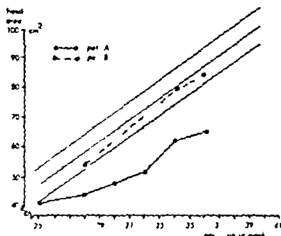
7 shows the head to chest relationship in both tients

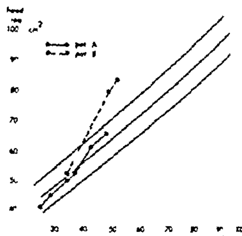
In the large for-dates group a normal fetal head e was related to a normal chest area in two cases the remaining 10 cases head size was normal =7) or large (n=3) in combination with a large st area Head to-chest relationship was always normal due to a relatively large chest

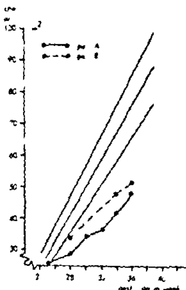
DISCUSSION

From our study on normal pregnancies it can be demonstrated that in the second trimester the fetal head area is larger than the fetal chest area In the third trimester because of accumulation of sub cutaneous fat and soft tissue during this part of pregnancy the chest area catches up with the head This can also be seen in the head to chest relation curve At term both dimensions are more or less of the same magnitude The increase in head area seems to tail off beyond 37–38 weeks In our study of small for-dates 2 types of fetal growth retardation could be recognized (Table III Figs 5 6 and 7) Similar patterns were described by Campbel (4) and Hansmann (11)

Asymmetrical growth retardation has been observed in experimental studies on impairment of vascular blood supply to the foetus in rats (19) sheep (7) and in monkeys (12 13 16) In these







Figs 5 6 and 7 Longitudinal follow-up of fetal head area (Fig 5) fetal ... area (Fig 6) and fetal head to-chest relationship (Fig 7) in a case of sym... (Pat A) and a case of asymmetric (Pat B) fetal growth retardation

...idies brain to body ratio was elevated suggesting brain sparing effect This might be due to a preferential redistribution of well-oxygenated blood to the fetal cerebrum Gruenwald s (9) pathologic findings in the human foetus confirm this type of growth retardation in relation to utero-placental vascular insufficiency

Symmetrical growth retardation is considered the outcome of a reduced growth potential as observed in malnourished rats (15 21) and malnourished guinea pigs (6 18) In the human foetus this type of growth retardation is seen after viral infection in early pregnancy and in the presence of chromosomal abberations There is a permanent loss of cells and the fetal brain is not spared In our study 10 out of the 21 cases of asymmetrical growth retardation were associated with pre eclamptic toxaemia or essential hypertension In the remaining 11 cases no vascular complications were observed In our group of symmetrical growth retardation twice a vascular factor could be demonstrated once ... was mitral stenosis and once a bicornuate uter... the remaining 3 cases no apparent reason for ... slow-down in fetal growth was found It seem... likely that fetal malnutrition as a result of a red... maternal caloric uptake plays an important ro... our part of the world According to our data ... asymmetrical type of growth retardation al... started in the last trimester of pregnancy in co... to the symmetrical type which started as early ... weeks of gestation The time of pregnancy in w... fetal growth retardation starts may be of ... tance in relation to the long term outcom of ... foetus Dobbing and Sands (8) described two ph... of human brain growth The first phase from ... 20 weeks of gestation consists of neuroblast ... liferation the second phase from 25 weeks of g... tion up to the second year of life reflects glial ... liferation

A long term follow up of the physical and m...

le III *Head area chest area head to-chest relationship and antenatal complications in the various weight categories in 59 complicated pregnancies*

of s	Head (B P D *) area (cm²)	Chest area (cm²)	Head to-chest relationship	Pregnancy duration (wks) during last ultrasonic measurement	Antenatal complications
mal weight group					
	Normal	Normal	Normal	33–39	P E T 9× Essential hypertension 4× Recurrent vaginal bleeding 2×
	Normal	<10th percentile	Abnormal	34–36	P E.T
*D group**					
	Normal	Normal	Normal	37	P.E T
	<10th percentile	<10th percentile	Normal	32–38	P E T 1× Essential hypertension 1× Mitral stenosis 1× Bicornuate uterus 1× None 3×
	Normal or <10th percentile	<10th percentile	Abnormal	33–39	P E T 9× Essential hypertension 1× None 11×
D group					
	Normal	Normal	Normal	35–36	None
	Normal	>90th percentile	Abnormal	37–40	Recurrent vaginal bleeding 1× Fetal hydrops 1× Abnormal G T T 2× None 3×
	>90th percentile	>90th percentile	Abnormal	33–38	Abnormal G T T

* T = pre-eclamptic toxaemia S F D = small-for-dates L F D = large for-dates G T T = glucose tolerance test.

velopment of the small for-dates newborn will e needed to evaluate the pattern of growth ardation described in this paper

n the 10 cases of growth acceleration head to-est relationship was asymmetrical i e the fetal est was relatively larger than the fetal head This ding suggests that fetal fatty tissue is particular ected in growth acceleration In 5 out of these 10 ces an abnormal glucose tolerance test was nd

It can be concluded that consecutive ultrasonic asurement of fetal head and chest size provides aluable information on the pattern of a developing al growth retardation or acceleration Furth nore consecutive measurement of fetal head l chest size will improve the pick up rate of ymmetrical growth retarded or accelerated in ts when compared with the estimation of fetal d size alone

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ENDOMETRIAL HISTOLOGY AND CIRCULATING LEVELS OF MEDROXYPROGESTERONE ACETATE (MPA) ESTRADIOL FSH AND LH IN WOMEN WITH MPA INDUCED AMENORRHOEA COMPARED WITH WOMEN WITH SECONDARY AMENORRHOEA

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act Circulating levels of medroxyprogesterone te (MPA) estradiol progesterone and gonadotrop- ere determined in 11 women on long term treatment depot MPA (Depo-Provera® DMPA) 150 mg i m 1 12th week as a contraceptive The women had iorrhoea due to the treatment Endometrial biopsy performed one week after injection and at the end of ? week period Blood samples were taken on the occasions The findings were compared with those untreated women having secondary amenorrhoea was still detectable in serum and the end of the 1? period Endometrial biopsies showed gestagenic ef in the second as well as in the first biopsy No MPA detectable in the untreated women with amenorrhoea no gestagenic effects could be demonstrated in their ies The estradiol levels in the DMPA group were in ange of the early follicular phase of a normal men- l cycle and showed a significant rise at the end of the ek period On the last sampling occasion the estra evels did not differ from those in the untreated wom- ith secondary amenorrhoea The levels of proges e and gonadotropins were in the range of the early ular phase in both groups These observations sup- that DMPA 150 mg i m every 12th week is a depot aration with prolonged effect and inhibits ovulation produces endometrial changes by means of biological tive serum concentrations throughout the 1? week d

pure gestagenic compound medroxyprogester acetate in a depot preparation (DMPA) has i in use as a contraceptive agent for about ten s It is generally administered in a dose of ng intramuscularly every 12th week The large ber of reports on its efficacy acceptability and effects have recently been reviewed (16 8)

DMPA 150 mg i m every 12th week is a contraceptive method as reliable as the use of combined oral contraceptive pills and has only few side-effects mainly bleeding disturbances During treatment there is during the first months unpredictable uterine bleeding which gradually ceases and most of the women thereafter develop amenorrhoea

Despite the extensive use of DMPA as a contraceptive the mode of action of the drug is not fully understood Its main mode of action seems to be inhibition of ovulation as it is shown (12 13) that it for at least three months abolishes the mid-cycle surge of the luteinizing hormone (LH) In addition it has a gestagenic effect on the cervical mucus and the endometrium

The period of time during which ovulation is inhibited is sometimes prolonged In a previous paper (5) we raised the question whether this prolonged inhibition of ovulation is due to individual differences in the rate of absorption at the site of injection i e due to an actual drug effect demonstrable for more than 12 weeks or due to hypothalamic suppression of varying duration caused by high initial serum levels of the drug which soon decrease to non-detectable concentrations The inhibition of ovulation within the scheduled 12 week period might also be due rather to such a prolonged hypothalamic suppression than to circulating levels of MPA at the end of the period

The aim of the present study is to clarify whether there are detectable levels of MPA in serum or demonstrable effects on the endometrium at the end of



Fig 1 Endometrial biopsy taken one week after injection in a DMPA treated patient showing atrophic endometrium with few and small glands having low epithelium and some stromal oedema (H E ×70)

12 week period in women with amenorrhoea ~ ing DMPA 150 mg i m every 12th week as a contraceptive and to compare these findings with untreated women having secondary amenorrhoea

MATERIAL AND METHODS

A total of 23 women were investigated Eleven of the women aged 24-4? (mean 31 8) received injections of DMPA (Depo-Provera®) every 12th week as a contraceptive They were studied during the 12 week period after having received 6 to 18 injections of DMPA (mean 12 8 injections) without interruption of the treatment and they all had amenorrhoea for at least 10 months During the period of the highest serum concentrations of MPA (6) blood samples from an antecubital vein were obtained on day 6-15 (mean 8 3) after the injection of DMPA On the same day endometrial biopsy specimens were obtained At the end of the 12 week period immediately before the subsequent injection of DMPA the blood sampling and endometrial biopsy were repeated

The other 12 women aged 19-39 (mean 25 ?) were all patients with secondary amenorrhoea from different causes The amenorrhoea had lasted more These women had never received any injecti and did not receive any therapy for their during the period of investigation In these women sample was taken and on the same day an biopsy was performed

All the blood samples were treated in The blood was collected partly in empty centrifuge partly in centrifuge tubes containing EDTA lant The samples were centrifuged and the ser plasma respectively were removed and stored until analyzed

The plasma samples were used for the assay FSH and the serum samples were u MPA estradiol and progesterone

The endometrial biopsy specimens were out anaesthesia or dilatation of the cervix curette according to Genell Biopsies were anterior and posterior wall of the uterine cav specimens were immediately fixed in 10% after preparation stained with haematoxy The sections were examined histologically morphological criteria of Noyes et al (15) al hou what modified The mitotic activity and vacuolation of the glandular epithel secretion were classified as absent or present of these parameters as used by Noyes et al (15) et al (7) was omitted

Medroxyprogesterone acetate was assayed by immunoassay (6) 0 1-1 0 ml of serum was extracted sensitivity was 50 pg No corrections were made fo cedural losses The antiserum against MPA was from Dr Kirton Upjohn Co Kalamazoo USA

Estradiol in serum was assayed by radioimmu according to Edqvist & Johansson (1)

Progesterone was determined by radio cording to Thorneycroft & Stone (20)

Plasma LH and FSH were determined in double antibody radioimmunoassays The previously reported in detail (19) In this assay standard for LH was equivalent to 55 ng of LER 10 mIU of the second IRP hMG and 1 ng of the for FSH was equivalent to 98 ng of LER 907 or 13 of the second IRP hMG The average met rors of the means of triplicated determination and 5 7 per cent for LH and FSH respectively range 1 0-20 0 ng/ml The normal range of LH and levels during the follicular phase in healthy w 0 5 to 3 0 ng/ml

RESULTS

MPA The serum concentration of MPA DMPA treated group about one week after jection was 3 57±0 51 (mean ±S E) ng/ml creased to 0 6±0 1 ng/ml at the end of the 1 period The decrease was highly significant 0 001) In the patients with secondary amenor without having received MPA no concentra MPA were detectable in serum

Estradiol The concentration of estradiol

Histological appearance of endometrial biopsy specimens in the two groups of women

		Patients given DMPA		Patients with secondary amenorrhoea
		1st biopsy	2nd biopsy	
ɔ of biopsies		11	11	12
successful :s		10	11	9
activity of lar epithelium	*Absent*	10	9	4
	Present	0	2	5
ial pseudo ication	Absent	10	9	1
	Present	0	2	8
ial vacuolation	*Absent*	8	6	7
	Present	2	5	2
lar secretion	Absent	8	5	7
	Present	2	6	2
l oedema	Absent	4	5	8
	+	6	5	1
	++	0	1	0
l decidual on	Absent	1	1	8
	+	7	4	1
	++	2	6	0

A group about one week after injection was 1 9 pg/ml and rose significantly ($p<0\ 025$) to 55 4±10 6 pg/ml at the end of the investiga In the untreated group of patients with secon amenorrhoea the estradiol concentration was 4 5 pg/ml and this level did not significantly 05) differ from the estradiol level in the A treated women at the end of the 12 week d The levels are in the range of the early fol ır phase of ovulatory women

ɔgesterone Serum levels of progesterone were v 0 6 ng/ml in the DMPA group one week after tion as well as at the end of the investigation serum levels of progesterone were below 0 6 l also in the patients with secondary amenor a

nadotropins The levels of gonadotropins on occasions in the DMPA group as well as in the ɔ of untreated women with amenorrhoea were e range of the follicular phase in normally truating women No difference between the entrations on the first (LH 0 9±0 1 ng/ml and 2 5±0 2 *ng/ml) and the second (LH 0 95±0 1* l and FSH 2 2±0 2 ng/ml) sampling occasion e DMPA treated group was found The go- tropin levels in the untreated group of patients secondary amenorrhoea were for LH 0 9±0 1 l and for FSH 2 1±0 2 ng/ml and these levels did not differ from those seen in the women re ceiving DMPA injections

Endometrial biopsy specimens The biopsies from patients given DMPA showed a marked atrophy of the endometrium (Fig 1) The glands were few with narrow lumina and the epithelium flattened and single layered with a marked reduc tion of the mitotic activity The stroma showed varying degree of oedema and decidualization The stromal changes however were less pronounced and tended to be rather focal When present decid ual reaction was usually seen around the blood ves sels In general the first and the second biopsy showed only minor histological differences

Table I summarizes the histological findings As can be seen the stromal decidual change tended to be somewhat more marked at the end of the 12 week period While invariably absent on the first biopsy occasion mitotic figures and pseudostratifi cation of the epithelial cells appeared in 2 cases at the end of the treatment period Signs of a weak secretory activity were noticed in 2 out of 10 cases on the first biopsy occasion but at the end of the investigation epithelial vacuolation had appeared in 5 and glandular secretion in 6 out of 11 biopsies

The histological diagnosis made on biopsies from the amenorrhoic patients were as follows resting endometrium or weak proliferative activity in 5



Fig 2 Endometrial biopsy from an amenorrhoic patient showing late proliferative phase (H E ×70)

cases normal proliferative phase in 2 cases and hyperplastic endometrium in 2 cases

Eosinophilic secretion like material was observed in some glands in biopsies from two patients and basal vacuolation was seen in occasional epithelial cells in biopsies from another two cases belonging to the series with proliferative activity or resting endometrium These changes were very weak and considered inconclusive for diagnosing secretory activity (Table I)

In 3 cases the biopsy specimens were inadequate for diagnosis The biopsies invariably differed histologically from those taken from the DMPA treated women (Table I and Fig 2)

DISCUSSION

The present investigation showed detectable concentrations of MPA in serum at the end of the 12 week period in women receiving 150 mg DMPA every 12th week as a contraceptive agent Furthermore endometrial biopsies showed mainly gesta-genic effects in specimens obtained at the e[nd of the] 12 week period as well as in specimens take[n] one week after the injection of DMPA

These observations support that DMPA [...] is a depot preparation with prolonged eff[ect ...] drug injected and that this prolonged effe[ct ...] for at least 12 weeks after injection of 15[0 mg] DMPA i m No detectable concentrations of [...] were found in the untreated women with a[menor]rhoea and no gestagenic effects were found [in] endometrial biopsy specimens

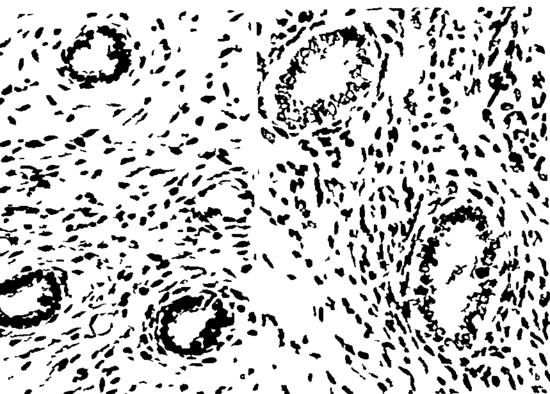
It is recently shown (Victor & Johansson [un]published) that even low concentrations be[tween] 0 5 and 1 0 ng/ml of MPA in serum are abl[e to in]hibit ovulation Therefore it seems probable [that] the main mode of action of DMPA in th[e above] mentioned dose is exerted by means of phy[sio]logically acting serum concentrations of [...] throughout the 12 week period

Gestagenic features can be shown at the e[nd of] the period clearly different from the end[ometrial] features in the patients with secondary a[meno]rhoea This strongly supports that the endo[metrial] changes in patients receiving DMPA as a co[ntra]ceptive result mainly from a direct effect of [con]tinued progestational stimulation and to a m[in]ser extent from the low production of endog[enous] estrogens which did not differ significan[tly be]tween the two groups

The endometrial histology in the DMPA tr[eated] women was mainly in accordance with pr[evious] studies on endometrial effects of Depo-P[rovera] (2 10 14)

In some cases signs of secretory activi[ty ap]peared in the endometrial biopsy taken at th[e end] of the 12 week period (Fig 3a and b) Pr[evious] studies (3 11) have shown the importance of e[stro]gens for the appearance of progesterone rec[eptors] in the endometrium In the present investig[ation a] significant rise in the serum concentration of e[stra]diol at the end of the 12 week period was f[ound] This increase might be sufficient to activate [pro]gesterone receptors to produce histological se[cretory] secretion in the presence of biologically a[ctive] serum levels of MPA The estradiol levels in th[e pa]tient whose biopsies are shown in Fig 3 we[re ...] and 46 pg/ml respectively on the two occasio[ns]

The finding of biologically active concentra[tions] of MPA in serum at the end of the 12 week p[eriod] does not exclude the possibility that hypotha[lamic] suppression induced by initially high con[...]



? Endometrial biopsy from a patient treated with A No signs of secretion in the first biopsy (*a*) basal lial vacuolation in the second (*b*) (H E ×448)

of MPA in serum can play a role in the pro- d inhibition of ovulation Kirton & Cornette easured serum levels of MPA in three patients 60 days after one single injection of 150 mg A The first ovulation after injection of MPA rred at very different levels of MPA in serum n one subject ovulation did not occur for more 100 days after drug concentration was non table Thus other mechanisms than actual effect is likely to be involved

e depressed levels of estradiol in serum about week after injection of DMPA corresponding ncentrations in the lower part of the normal in the normal early follicular phase (9) and ibsequent rise at the end of the 12 week period accordance with previously published investi ns (5)

agreement with previous reports (4) the basal tion of gonadotropins was not affected during nent with DMPA and the plasma levels did iffer from those in untreated women with sec ry amenorrhoea

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A RADIOIMMUNOLOGICAL METHOD FOR OESTRONE

Plasma Levels of Non conjugated Oestrone during Uncomplicated Pregnancy

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ract A specific antiserum to oestrone[1] has been used levelop a radioimmunoassay No chromatographic ration step was included A small amount of plasma 1–0 15 ml) was extracted once with diethyl ether The iod was used to estimate plasma levels of non-con ted oestrone in women during uncomplicated late nancy The oestrone plasma concentrations showed a ual increase from a mean of 4 ng/ml in the 2?nd week 1 ng/ml in the 41st week Great individual variations found No systematic changes of unconjugated rone plasma concentrations were noticed during a 24 period in late pregnancy Short term studies revealed large and rapid fluctuations may appear in the levels nconjugated oestrone during pregnancy

1y studies have been performed on biosynthesis ary excretion and plasma concentrations of trogen hormones during human pregnancy The rrelation between mother fetus and placenta in trogen synthesis and metabolism has been eluci d The introduction of the concept of the feto-ental unit (7) has turned out to be fruitful for understanding of the oestrogen metabolism in 1an pregnancy Still the knowledge of the siological role of oestrogens in gestation is ted

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ie following abbreviations and trivial names are used rone=3 hydroxy 1,3,5(10)-oestratrien 17-one oest ol 17β=1,3,5(10)-oestratriene 3 17β-diol oestriol= 5(10)-oestratriene 3 16α 17β-triol androstenedione= drostene 3 17-dione cortisol=11β 17α 21 trihyd -4-pregnen 3 0-dione 17α hydroxyprogesterone= hydroxy-4 pregnene 3 20-dione progesterone=4 gnene 3,20-dione testosterone=17β-hydroxy-4-andro- 3-one 16α hydroxyoestrone=3 16α-dihydroxy 1 3,5 -oestratrien 17-one

Oestrone plasma or blood levels have earlier been studied by various methods Roy & Brown (26) used a colorimetric method Preedy & Aitken (25) and Ittrich (16) described fluorometric methods Svendsen (30) and Baird (4) developed double isotopic derivative methods Later the technique of gas chromatography was used by Adlercreutz (1) and Fischer Rasmussen (12) Attal et al (3) de scribed a way for determination of oestrone with electron capture detection In the nineteen seven ties a competitive protein binding technique was used for the estimation of oestrone plasma levels (14 28 33)

In recent years radio-immunoassays have been developed for measurements of oestrogens in blood Since no specific antibody to oestrone has been available previous methods have included a separation step in most cases some kind of chroma tography (10 11 18 19 22 24 34 35)

In 1974 Lindberg et al (22) published radio-im munological methods for estimating unconjugated oestrone oestradiol 17β and oestriol Their report included studies of oestrogen plasma levels in women with uncomplicated and high risk preg nancies (20 21) At that time no specific oestrone antibody was available The present investigation was done with the same specific antiserum as that used by Brenner et al (5) to develop a method for the estimation of oestrone in plasma during preg nancy Thus it will be a complement to the works of Lindberg et al This report will present the meth od and give plasma levels of non-conjugated oestrone during late normal pregnancy Circadian and short term variations were also studied

Table I *Per cent crossreaction with the oestrone antibody*

Test substance	Per cent crossreaction
Oestrone	100
Androstenedione	<0 1
Cortisol	<0 1
17α hydroxyprogesterone	<0 1
Oestradiol 17β	3 3
Oestriol	1 4
Progesterone	<0 1
Testosterone	<0 1

MATERIAL AND METHODS

Steroids

(2 4 6 7)-³H oestrone (S.A 115 Ci/mmole) was obtained from New England Nuclear Corp Boston USA Non radioactive oestrone oestradiol 17β oestriol 17α hydroxyprogesterone androstenedione progesterone and testosterone were supplied by Ikapharm Ramat-Gan Israel Non-radioactive cortisol was obtained from Sigma Chemical Company St Louis Mo USA The antiserum was supplied by Dr Jean Pierre Raynaud the Roussel Uclaf Research Centre France Without any pretreatment the antibody was diluted to 1 10 000 in phosphate buffered saline (PBS) containing 0 1% gelatin and stored at 4°C

Reagents

Special chemicals were obtained from the following sources Charcoal (Carbo medicinalis Nord) Apotekarnas AB ADA Gothenburg Sweden Dextran 70 from Pharmacia Fine Chemicals Uppsala Sweden (Favorigelatin) from AB Törsleff Co Stockholm Sweden Naphthalene from Packard Inc Downer Grove USA Omnifluor from New England Nuclear Corp Boston USA

Reagent grade absolute ethanol dioxane and diethyl ether from freshly opened cans were used without any additional purification Phosphate buffered saline containing 0 01 M sodium phosphate (pH 7) 0 14 M sodium chloride 0 01% merthiolate was used as the diluent solution Buffer containing 0 1% gelatin was used to dilute the antibodies Dextran-coated charcoal suspension was made by adding 2 5 g charcoal and 0 25 g Dextran T 70 to 1 000 ml PBS

Assay method

Hotchkiss et al (15) and Edqvist & Johansson (10) described a method for measurement of oestradiol 17β With minor modifications the same procedure was used for the oestrone measurement in the present investigation When analysing plasma from pregnant women volumes of 0 01–0 15 ml were used Plasma was extracted with 1 ml of diethyl ether by shaking on a Vortex mixer The ether solution was decanted after freezing of the aqueous layer The recovery after this extraction step was 75 3% When the method was used for plasma from women a volume of 0 4 ml was used Plasma ed with 10 volumes of diethyl ether by intermi for 1 min The supernatant was withdrawn by The recovery with this procedure was 90 7% nique to withdraw the diethyl ether gave higher also when smaller plasma volumes were used T sion however was then not acceptable

The supernatant was evaporated to dryness and of the antibody solution was added to each tube tubes were briefly shaken and incubated for 30 room temperature After incubation 100 µ solution was added to each tube This solut 400 pg (2 4 6 7)-³H oestrone (~12.5 µCi) The of the tubes were briefly mixed and incubated at 4 C in a refrigerator Free and bound steroids separated by the dextran-coated charcoal techniq

Counting was performed on Packard Tri-Carb scintillation spectrometers (Model 3310 and 3??) counting efficiency was 25 and 40% respectively scintillation solution contained 100 g naphtha omnifluor in 1 000 ml dioxane

Standard samples made up with p 25 50 100 250 500 and 1 000 pg in duplicate) cessed simultaneously for each set of sample

Evaluation of the method

Specificity The specificity of the antibody assaying known amounts of different test sub the method The percentage cross reaction at 50% displacement of the tracer The re Table I

Different volumes of pooled plasma samples from menopausal and postpartum (5–6 days after de women were extracted with 10 volumes of diethyl and analysed The values obtained were superim

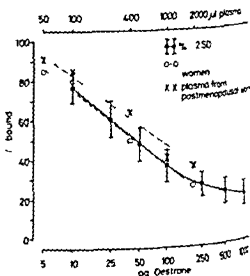
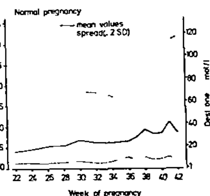


Fig 1 The mean and spread (±2 S D) of 57 curves prepared over a period of 16 months 0 (no added unlabelled steroid) has been set to



2 Plasma levels of non-conjugated oestrone during
mplicated pregnancy The spread (±2 S D) was cal
ed after a logarithmic transformation of the original
es In this and the following figures a scale of nmol/l
ded

e standard curve of oestrone (Fig 1) The oestrone
measured in plasma from postpartum women was 71
l and the level in plasma from postmenopausal wom-
as 45 pg/ml

curacy The accuracy of the method appears from
e II where recovery experiments are shown Known
unts of oestrone were added to 50 µl of plasma from
partum women Acceptable accuracy was obtained
in the working range

nsitivity It was found that values of 1 pg of oestrone
ore were significantly different from zero (Table II)
amples assayed were well above the limit of detec
The effect of reagent blank was minimized by adding
of diethyl ether to the standard tubes The plasma
k was considered as negligible (Fig 1)

ecision The within assay variation was calculated
the differences between duplicate determinations of
plasma samples according to Snedecor (29) The
lts are given in Table III

or calculation of the between assay variation a plasma
containing a known amount of oestrone (10 ng/ml)
assayed 57 duplicate measurements were performed
coefficient of variation was 16 1%

he variation between standard curves over a long
od (Fig 1) indicated the importance of preparing
dard curves with each set of samples assayed

ects

en women were followed from the 22nd week of preg
y till delivery Sampling was performed every second
k from the 22nd to the 36th week and then every week
ples were also collected from a number of women
ing the municipal antenatal clinic in Uppsala in the
24th 26th 36th 37th 38th etc week of preg
y Most women contributed only one sample but a
two to three at different stages of gestation All wom
were in general good health with regular menstrual
es The date for the last menstrual period was known
pregnancies were uncomplicated and resulted in the

Table II *Recovery of oestrone added to 50 µl of plasma from postpartum women*

Correction was made for procedural losses CV is coefficient of variation 6 assays were performed at each level

Amount of oestrone added in pg	Per cent recovery: Mean with 95% confidence limits	CV
1	236±151	61
2.5	113± 41	34 8
5	106± 25	22 9
10	108± 48	42.5
25	112± 9	7 7
50	95± 11	11.3
100	77± 5	6 3
250	71± 23	30.3
500	84± 22	24 6

birth of single healthy infants with a birth weight exceeding 2 500 g No significant differences in the plasma oestrone levels were found between these two series of women The results were thus pooled for calculating means and normal limits in the various weeks of pregnancy

Circadian variations in oestrone plasma levels were studied in six women In four women venous samples were taken every fourth hour in two cases every second hour Two patients had mild pre-eclampsia At the time of sampling however the symptoms had disappeared

Short term variations were studied in five women Samples were collected every five minutes during one hour Four of these women had mild pre-eclampsia

Venous blood was collected in heparinized tubes Plasma was separated by centrifugation and stored at −20°C until assayed

Statistical methods

As the distribution of the values in the various weeks of pregnancy displayed a positive skewness normal limits were calculated after a logarithmic transformation of the original values $Y = \ln x$ where x is the observed value Upper limit$=e^{y+2s}$ and lower limit$=e^{y-2s}$ (13)

Table III *The precision of the oestrone measurements at different levels*

Range (ng/ml)	Coefficient of variation (%)	Number of duplicate determinations
0– 5	17 8	15
5 1–10	12 9	46
10 1–15	11 6	72
15 1–20	14 7	43
>20	16 0	53

Table IV *Plasma levels in ng/ml of non-conjugated oestrone during uncomplicated pregnancy*

Upper and lower limits (±2 S D) were calculated after a logarithmic transformation of the original values

Week of pregnancy	No of samples	Mean	Upper limit	Lower limit
22	30	4 1	10 2	1 3
24	30	4 7	12 2	1 3
26	29	5 4	16 8	1 2
28	30	5 4	14 7	1 4
30	30	6 8	18 6	1 8
32	30	6 3	18 4	1 4
34	30	6 2	17 4	1 6
36	29	6 6	13 3	2 8
37	30	7 7	20 6	2 0
38	30	9 4	24 2	2 8
39	29	8 4	22.8	2 2
40	29	8 6	22 8	2 4
41	30	11 1	30 7	2 9
42	15	8.5	31 5	1 4

RESULTS

The plasma levels of non-conjugated oestrone during uncomplicated pregnancy are shown in Table IV Fig 2 From week 22 to week 36 there was a slow increase from a mean of 4 1 ng/ml to 6 6 ng/ml Thereafter the mean level increased somewhat more rapidly to 11 1 ng/ml in the 41st week In week 42 the mean level decreased to 8 5 ng/ml At this stage of gestation however only 15 samples were available for analysis The lower normal limit showed a slow increase from 1 3 ng/ml in the 22nd week to 2 9 ng/ml in the 41st week The upper limit increased about threefold from about 10 ng/ml to 30 ng/ml during the same period

Plasma concentrations of non-conjugated oestrone recorded for individual women four throughout pregnancy are graphically described in Fig 3 Generally the values of the same were to be found in the same range of the n curve throughout pregnancy

Circadian variations in plasma levels of non-conjugated oestrone during 20–30 hour periods shown in Fig 4 No evident changes correl time rest or meals could be found The m difference between oestrone levels measured in same individual was 5 8 ng/ml The results of shortterm studies are given in Fig 5 The ma difference between concentrations measured in individual during one hour was 11 6 ng/ml In woman the oestrone values were found to be the lower limit of the normal curve This patient mild pre-eclampsia but showed no symptoms at time of sampling Later she gave birth to a infant weighing 3 020 g

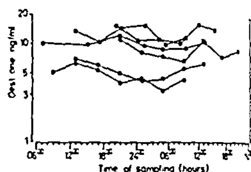


Fig 4 Variations in the plasma levels of non-conj oestrone during 20–30 hour periods in six pregnant in the last trimester A logarithmic scale is used

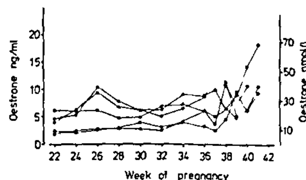


Fig 3 Plasma levels of unconjugated oestrone in five healthy women followed throughout pregnancy The remaining ten patients showed similar patterns

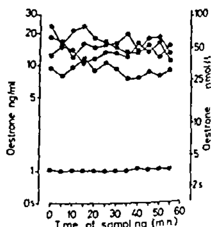


Fig 5 Variations of non-conjugated oestrone in during one hour in five pregnant women in the last trimester A logarithmic scale is used

DISCUSSION

t previously published radio-immunoassays for rone have included a laborious column chrom raphy (5 10 11 24 34 35) In efforts to com - rapid techniques some authors omitted the omatography (10 11) and measured immuno- tive oestrogens rather than oestrone with fair non specific antisera In the present study a o-immunological method for the assay of plas oestrone omitting the chromatographic step been developed Due to the high specificity of oestrone antiserum used in the present study trone plasma concentrations can be measured hout prior separation of the plasma oestrogens s was true also with a method recently published Doerr (8) The oestrone antiserum used in our oratory crossreacts with oestradiol 17β and triol to a minor degree Since the plasma levels non conjugated oestradiol 17β and oestriol are stantial during late pregnancy (20) the method give a slight over estimation of the plasma trone levels The results are however present without correction for this over estimation and hout correction for procedural losses If correc s were done only small differences in the final ome should be noticed By the omission of e corrections the procedure becomes faster and e simple In another publication (5) a crossreac of 3 per cent with 16α hydroxyoestrone was re ted for this antiserum Since the plasma level of conjugated 16α hydroxyoestrone is low during gnancy (2) the interference of this hormone is ligible

he plasma levels of oestrogens during preg cy have been the subject of many investigations st of these reports however have dealt with triol and oestradiol For references see (20)

Most investigations of the blood concentrations oestrone during pregnancy have revealed a slow ease of the oestrone level throughout preg cy This was true for unconjugated (6 9 20 23 as well as total (unconjugated+conjugated) trone (17 27) Svendsen & Sorensen (31) found ncrease in oestrone levels up to the last stage of tation where the concentrations remained con it or showed a weak tendency to decrease her Rasmussen (12) presented an extensive in tigation of total oestrone in plasma He found no nificant increase in plasma oestrone during late gnancy Three women however showed very high values If these values were neglected a signi ficant increase was evident

Our results are in agreement with previous stud ies in that we found a slow increase during late preg nancy and large individual variations Our estima tions of non conjugated oestrone in plasma are in the same range as the results of Svendsen & Soren sen (31) Tulchinsky et al (32) Loiraux et al (23) Lindberg et al (20) de Hertogh et al (6) and Du mont et al (9) These groups used a double isotopic derivative method (31) a radioligand assay (32) and radio immunological assays (6 9 20 23) respec tively Roy & Mackay (27) could not demonstrate any significant changes of total oestrone levels in blood during a 24 hour period Our circadian and shortterm studies reveal that the levels of uncon jugated oestrone may show large and rapid varia tions No systematic patterns in the fluctuations could be noticed during a 24 hour period The rapid variations may be explained by the assumption that the degree of conjugation undergoes rapid changes

The aim of this study was to develop a simple and reliable method for the measurement of uncon jugated oestrone It is known that the main part of plasma oestrone in human pregnancy is conjugated (23) Maybe the plasma levels of unconjugated and conjugated oestrone would give a more representa tive picture of the oestrone production in placenta By introducing a hydrolysis however our proce dure would become more time-consuming and thus less suited for clinical purposes

This description of plasma levels of oestrone dur ing normal pregnancy will serve as background data for investigations of oestrone in pathological preg nancies

ACKNOWLEDGEMENTS

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HETEROLOGOUS GROWTH OF HUMAN OVARIAN CANCER

A New in vivo Testing System

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tract Successful heterotransplantation of ovarian ...er in the mouse mutant *nude* is described with serial smission in one case to date Light and electron roscopic examination of this tumour a poorly dif ntiated adenocarcinoma has not revealed any altera in its morphology after six passages Tumour bearing e have been treated with ThioTEPA or 5 Fluoro- .cil in an attempt to see if they show a similar effect to seen in the patient ThioTEPA resulted in a marked ession whilst there was no effect from 5 Fluoro- icil on tumour growth—confirming the ThioTEPA ct seen in the patient

.ny drugs are used in clinical practice to treat lignant ovarian disease with widely varying .nour response Because of this unpredictable be viour many investigators have been engaged in rk trying to predict the response of individual nours to various forms of therapy—especially motherapy Among systems used are short m monolayer tissue culture organ culture and rerotransplantation—rendering the animal im ino-incompetent first Therapy based on results om these systems has not been successful in alter the clinical course of the disease

The mouse mutant *nude* (athymic) is a new and luable tool in studying human tumours Mice with is mutation lack a thymus (and so T lympho- tes) and are thus immunologically incompetent gaard & Povlsen (1 2) have transplanted and idied several tumours in these mice and have monstrated conclusively that the mice are unable reject the foreign tissue Further after passaging tumours have maintained their integrity both orphologically and biochemically The impor nce of these mice which need no irradiation or chemical immunosuppression to act as host to tu mour heterotransplantation in the research of var ious modalities of therapy is illustrated in this pre liminary report of our experience of growing ovar ian cancer and testing cytostatic drugs against it One case is presented in detail

MATERIALS AND METHOD

We obtained tumour tissue at laparotomy from patients suffering from ovarian cancer Surgery was performed as a primary procedure with radiotherapy or chemotherapy to follow Within an hour of surgery representative non necrotic areas of the tumour were chopped into small pieces (2 mm diameter) and implanted subcutaneously in to the mice Tissue was also sent for light and electron microscopy When the tumour had grown to 0 5–1 cm dia meter it was transplanted into 30 mice ready for experi mentation

Mice

We used young females weighing 20 g nu/nu/BALB/c/ BOM stored on an air flow bench in a conventional mouse room at 28 C and fed standard pellets and tap water ad lib

Drugs

The drugs tested have in the first experiment been re stricted to those in clinical use in patients with ovarian cancer at the Norwegian Radium Hospital—ThioTEPA and 5-Fluoro-Uracil

ThioTEPA (Tifosyl®) was obtained as a powder in 10 mg vials This was dissolved in physiological saline for a regimen of 4 mg/kg/day intraperitoneally for 5 days with a two week pause between treatments

5 Fluoro-Uracil (Fluoro-Uracil®) was obtained in am poules containing 250 mg in 5 ml This was diluted in phy siological saline for a regimen of 25 mg/kg/day intra muscularly for 5 days also with a two week pause

The control group received 0 1 ml saline intraperitone ally in the same manner

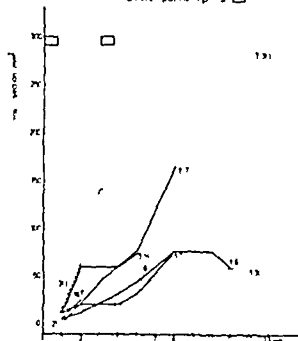


Fig 1

Assessment

The efficacy of therapy was assessed by measuring two diameters of the tumour weekly and calculating the cross section A control of drug toxicity was made by weighing the animals weekly At the conclusion of the second course of treatment mice from each group were sacrificed d tissue prepared for both light and electron micro-py

Electron microscopy

Representative 1 mm cubes of tissue were fixed in 2% phosphate buffered glutaraldehyde postfixed in osmium tetroxide dehydrated through graded alcohols and embedded in EPON 812 using propylene oxide as an inter medium Semithin sections were made with an LKB Pyramitome equipped with glass knives and stained with toluidine blue for light microscopical orientation Ultrathin sections were cut with glass knives mounted on an LKB *Ultratome III* collected on naked copper grids stained with uranyl acetate and lead citrate and examined in a Philips EM 301 electron microscope

Case history

The patient whose tumour was studied was a 53 year old para 4 whose menopause at the age of 47 had been unremarkable In September 1973 she had noticed increasing abdominal distension and intestinal colic Three months later she consulted her doctor because of breathlessness and a 5 kg weight loss He found ascites a left sided pleural effusion and an abdominal tumour filling the whole pelvis extending up to the umbilicus and fixed to the pelvic wall At laparotomy the peritoneal cavity was filled with a tumour arising from the ovary The omentum was ily infiltrated A biopsy was taken and tissue as described Malignant cells were found in the fluid and the case was classified as a stage IV cancer and treatment begun with ThioTEPA. She remained well on regular ThioTEPA until June 197 she developed ascites and symptoms of a subacute obstruction *In view of her poor prognosis treatment* palliative She died in August of bronchopneumonia wide spread metastases from her ovarian cancer months after initial therapy

RESULTS

To date we have transplanted tissue from mours with successful growth in all ex These 3 failures were at the beginning of our and we feel that experience gained earlier now us in the selection of cancer tissue

Initially there was a lag period of 3 to 4 m before the tumour showed appreciable growth *following this growth rate was steady* In the second passage the rate was faster In the case under review 20 mice received tumour pieces the first passage subcutaneously and af weeks 17 had visible tumours whilst 10 mice received a minced cell suspension and here it 6 weeks for 5 mice to develop a tumour of com

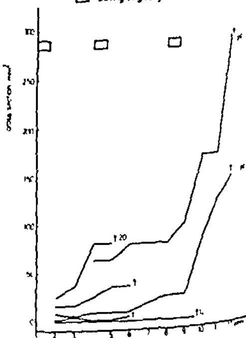
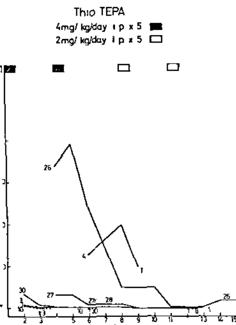


Fig 2



size Unfortunately not all the animals were fully healthy and several died of natural s The life span of these mice varies greatly t has been found that they die of a wasting syn e so it is very important that they be as uni in size and health as possible at the beginning experiment

ol group

5 mice in this group received saline and their urs continued to grow at a steady rate (Fig 1) died after 4 weeks

5 Fluoro-Uracil group

Of the 6 mice in this group one died in the third week and two in the seventh Those surviving showed a continued steady growth of tumour (Fig 2)

ThioTEPA group

Despite careful toxicity studies beforehand 3 mice died before they received their second course thus the dose was halved from 4 mg to 2 mg/kg/day for 5 days Tumour growth is shown in Fig 3 This study ended after only 2 courses as at this time one could see a clear difference in the growth pat terns following the use of the two drugs and we wanted to sacrifice some mice for histology whilst there was still some tumour present in this last group

Remaining ThioTEPA mouse

At the conclusion of the experiment one mouse was alive—with complete regression of the tumour This mouse had received 4 mg/kg/day for 1 course and 2 mg/kg/day for 2 courses Eight weeks after the cessation of the last course the tumour had grown almost as large as it had been at the begin ning of the experiment We gave a further 3 courses of ThioTEPA—see Fig 4—with obvious effect but less marked than the initial effect After the third course the mouse appeared to be wasting so in jections were stopped—and the mouse continued to thrive so we concluded that toxicity had played a part Once more the tumour began to grow—but the mouse died before we could give further drug suddenly after 37 5 weeks

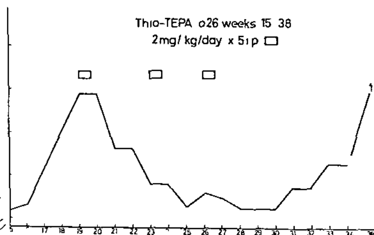


Fig 4

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ECTOPIC PREGNANCIES AND THE USE OF INTRAUTERINE DEVICE AND LOW DOSE PROGESTOGEN CONTRACEPTION

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ict In a series of 71 ectopic pregnancies ten were ated with the use of an intrauterine device (IUD) ree with the use of low dose progestogen contracep- or comparison a series of 800 legal abortions were d and in 20 of these cases pregnancy originated an IUD was in utero and in 13 during the use of low ontraceptive pills When using the above mentioned iceptive methods the possibilities of an ectopic preg should be taken into consideration

arly as 1929 Grafenberg reported (4) ectopic iancies in connection with the use of IUDs iuterine contraceptive devices) and it has been ved that pregnancies which occur during the f IUD s show a greater tendency to be ectopic pregnancies which occur when IUD s are not used (6) Recently attention has been also paid to the fact that ectopic pregnancies have occurred during the use of low dose progestogen contraception (1 2 3 5) Because both of these contraceptive methods are widely used in our area and an ectopic pregnancy may be a dangerous condition we have in this study examined to what extent ectopic pregnancies treated in our hospital have originated during the use of these contraceptive methods

MATERIAL

From 1972 to 1974 a total of 9016 mothers were delivered *in the area in which this material was collected* During this period 71 ectopic pregnancies were treated surgically which corresponds to 7 8 ectopic pregnancies per 1000

I *Patients*

it	Age (y)	Number of previous abortions	Number of previous deliveries	Period of use of contraceptive method (months)	The name of IUD or progestogen used	Endometrial histology	Result of immunological pregnancy test
	38	–	3	72	Lippes Loop	–	Pos
	31	1	1	36	Lippes Loop	Secretory	Neg
	31	1	3	2	Lippes Loop	Secretory	Neg
	35	–	1	36	Previgon	Decidual reaction	Neg
	28	–	4	18	TCu 200	Secretory	Pos
	35	–	2	3	Progestasert™65	–	Pos
	24	–	2	18	Lippes Loop	–	Pos
	35	1 (legal abortion)	3	60	Gravigard	–	Pos
	26	–	0	2	TCu 200	–	Pos
	38	1	2	14	TCu 200	Secretory	Neg
	24	–	3	8	Lynestrenol	Proliferation	Neg
	20	–	2	3	Norethisteron	Proliferation	Neg
	35	–	3	6	Norethisteron	Decidual reaction	Neg

deliveries Investigations were made to ascertain to what extent ectopic pregnancies originated during the use of IUDs or low dose progestogen contraception

Furthermore for comparison all legal abortions carried out in 1973 were studied to find out how many of these pregnancies originated during the use of IUD or minipills (low dose progestogen contraception)

RESULTS AND COMMENTS

In Table I the patients with ectopic pregnancies associated with the use of IUD or low dose progestogen contraception from 1972 to 1974 are presented The number of IUD users was 10 and the average age of these patients was 32 years Only one of these patients had no previous pregnancies and among the others the number of previous pregnancies ranged from one to four Three patients had previous spontaneous abortions and one had a previous legal abortion The period of IUD use ranged from two months to six years being on an average two years and two months The IUD trade marks were as follows four cases of Lippes Loop three of Copper T (T Cu 200) and one of Previgon Progestasert TM65 (ALZA s progesterone uterine therapeutic system) and Gravigard In four patients preoperative curettage showed secretory endometrium and four patients had negative results from immunological pregnancy tests

There were only 3 confirmed users of low progestogen pills The average age of these patients 26 years and the average period of use was 6 onths One of these used Lynestrenol (0 5 mg) and two Norethisterone (0 3 mg)

During the year 1973 a total of 800 legal abortions were performed in the area in which this material was collected In 20 of these cases pregnancy originated while an IUD was in the utero In addition 13 patients had regularly used low progestogen contraceptive pills During the same year 28 cases of ectopic pregnancies were treated at Oulu University Hospital and of these there were four pa... IUD in utero and two patients were regular... low progestogen contraceptive pills (... one) Thus among the IUD users f... nancies corresponded to 20 legal abortion and among the users of low proges ogen ... ectopic pregnancies corresponded to 13 legal ...tion patients

Since we have observed 13 ectopic ... connected with the use of IUD or proges... contraception we agree with Hawkin... that in patients of abdominal pain who ... these contraceptive methods the possibili... ectopic pregnancy should be taken into con... tion Also of importance are the facts tha... material diagnostic expedients gave negat... in some cases and in two cases a dangerous ... cation was in the process of developing

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VALUE OF EXTERNAL VERSION IN FETAL MALPRESENTATION IN COMBINATION WITH USE OF ULTRASOUND

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ct During 1969–1974 six hundred and forty nine ex versions were attempted during the last trimester on others with fetal malpresentation The procedure onitored with ultrasound in 1969–1974 Most of at (70 0%) were made during the 32nd–36th weeks nal version rate after one or more attempt was being lower (67 0%) in nulliparous than parous 1 (84 6%) The incidence of breech presentation at decreased from 4 5 to 2 9% ($p<0\ 001$) The most s complication was one premature labor but the in rvived The perinatal mortality was 2 0% and after ing abnormal infants 0 8% The combination of al version and the use of ultrasound is a safe method avoids hazardous vaginal breech delivery and is mended in obstetric practice

perinatal mortality and morbidity rates associ vith vaginal breech delivery have been docu d repeatedly (5 10 12 15 17) During the ital period only the major complications are ted whilst minor damage may not be evident ater as mental and motor sequelae (14 16 20) outine use of abdominal delivery although it ases the fetal risks may increase maternal dity and morbidity and create potential haz n subsequent pregnancies

uncomplicated external version obviates all sks associated with vaginal breech delivery creased the number of caesarean sections be of breech presentation Since the year 1969 ve attempted external versions in fetal mal ntations in utero This study was initiated the introduction of ultrasound equipment into e obstetric practice in our hospital Such ap is is of value in diagnosis of fetal presentation umber as well as placental site Our results 6 years are summarized in the present report

PATIENTS AND METHODS

From 1969 all maternity welfare units in our region were instructed to direct the mothers whose fetal presentation was not cephalic or was uncertain during the 32nd week or later to our specialized maternity unit for external fetal version To the end of 1974 491 women with fetal mal presentation have been collected This represents 2 6% of 18 783 singleton deliveries in our unit during the study pe riod The exact position of the fetus and placental site were detected in most cases (89 0%) with ultrasound (Kretztechnik 4100 MGS) A breech presentation was diagnosed in 95 9% and a transverse lie or combined mal presentation in 4 1% 50 1% of patients were nulliparous

The study was performed on an out patient basis After emptying the urinary bladder the mother rested on her back with partially flexed thighs The breech was dis placed upward from the maternal pelvis and laterally to the side of fetal back The fetal head was pushed to the opposite side and downward by the other hand The per formance was gentle and any force especially against the placental site was avoided No vaginal manipulation was allowed Sometimes one must wait for up to 10–15 min before the fetus own movements complete the version If the fetus could not be turned in this direction an at tempt was made in the reverse direction Cardiotoco graphic recording of fetal heart rate (FHR) and uterine contractions before and after the attempt was performed routinely The success of version was confirmed by ultra sound if uncertain by palpation

Attempts at version were made once in 378 cases twice within 1– weeks interval in 73 cases three times in 37 cases four times in two cases and six times in one mother yielding a total of 649 attempts The intramuscular admini stration of spasmolytic analgesic or tocolytic drugs (diaz epam 10 mg pethidine 50 mg or isoxuprine 10 mg) was used in 13 9% of cases before the 1st attempt and in 33 3% of cases before the later ones No anesthesia was ever given

Absolute contraindications to version were total or par tial placenta praevia multiple pregnancy rupture of mem branes labour and contracted pelvis necessitating caesar

Table I *Relationships between gestational age attempt and result of version as well as occur spontaneous reversion (to breech) or version (to vertex)*

Weeks of pregnancy	Number of attempts	Successful result		Spontaneous reversion		Unsuccessful result		Spontaneous version	
		No	%	No	%	No	%	No	%
28	2	2	100	-		-		-	
29	3	3	100	-		-		-	
30	11	10	91	-		1	9	1	100
31	11	7	64	1	14	4	36	2	50
32	43	35	81	-		8	19	1	12
33	9	64	69	9	14	28	31	2	7
34	115	84	73	12	14	31	27	2	6
35	107	70	65	7	10	37	35	-	
36	94	49	52	3	6	45	48	2	5
37	71	34	48	2	6	37	52	2	5
38	66	29	44	2	7	37	56	1	5
39	18	10	56	-		8	44	-	
40	10	4	40	1	25	6	60	-	
41	4	1	25	-		3	75	-	
42	2	1	50	-		1	50	-	
Total	649	403	62 1	37	9 2	246		13	53

ean section apart from the fetal presentation Previous caesarean section or other uterine scar or anomaly were regarded as relative contraindications

RESULTS

Incidence of breech presentation at birth

The incidence of breech presentation at birth was 4 5% among 15 279 singleton pregnancies prior the study in 1965-1968 and during the study 2 9% among 18 783 parturients The decrease of 1 6% is highly significant ($p<0\ 001$)

Gestational age at version

All the attempts in relation to gestational age are given in Table I Most attempts (70 0%) were made during the 32nd-36th weeks Twenty seven versions (4 2%) were tried before the 32nd week and six (0 9%) after the 40th week The mean pregnancy duration during the 1st attempt was 34 8 weeks (range 28-42) during the 2nd 35 7 (range 31-38) and during the 3rd 37 0 (33-41)

Success rate

The success rate (per cent) in relation to gestational age is shown in Table I The mean was 62 1% The 1st attempt was successful in 66 7% and the 2nd and 3rd in 43 6% The final turning rate after one or more version in the series was 76 2% and was lower (67 0%) in nulliparous than parous women (84 6%) ($p<0\ 001$) The rate of success decreased somewhat with advancing gestational age However differences between various weeks (until the showed a small ($p<0\ 05$) if any significan size (height or weight) of the mother and the success rate were not related The various placental sites interior (40 2%) posterior (46 1%) or wall (12 3%) or lower segment (1 4%) did not influence the version rate

Spontaneous version

Spontaneous version occurred 50 times in 4 ers (Table I) After successful external version reversions to breech occurred in 33 mothers is 9 2% of all successful versions Because

Table II *Complications in 491 mothers in a tion with 649 successful or attempted exter sions (% out of 649 versions)*

Complication	No	%
Uterine contractions	27	4 2
Uterine bleeding	3	0 5
Uterine bleeding and contractions	2	0 3
Variation in FHR (over <100 or >160/min)	3	0 5
Rupture of membranes and labour	1	0 2
Abruption of placenta	0	0
Fetal death	0	0
Total	36	5 5

III *Duration of pregnancy and method of delivery in mothers with breech or vertex presentation at*
and overall

	Breech presentation (N=117)		Vertex presentation (N=374)		Overall (N=491)	
on of pregnancy						
er the 36th week	2	(1 7%)	2	(0 5%)	4	(0 8%)
ng the 36–37th week	8	(6 8%)	10	(2 7%)	18	(3 7%)
r the 42nd week	1	(0 9%)	3	(0 8%)	4	(0 8%)
n	39 6	(range 32–43)	40 8	(range 34–43)	40 0	(range 3 –43)
d of delivery						
inal	82	(70%)	357	(95 8%)	439	(89 7%)
arean section	35	(30%)	17	(4 5%)	52	(10 3%)

l version was repeated only 10 women with aneous reversion still had breech presentation th which is 2 5% of successful versions Thir versions to vertex occurred after one unsuc ul attempt in nine cases two attempts in three and three attempts in one case The rate of aneous version was 5 3 per cent of all unsuc ul attempts Of all spontaneous versions or sions 13 (26%) occurred after the 35th week (16%) after the 36th week and four (8%) af e 37th week One reversion was detected in VI even during the 40th week

plications

complications were mostly mild uterine con ions (Table II) In five cases slight uterine ling occurred but ceased within 1–3 days In cases the FHR varied significantly (<100 or /min) but returned to normal 8–14 hrs later healthy infants in vertex presentation were born at term In one case the membranes ruptured 12 hrs after successful version during the 34th week and the delivery took place two days later The infant survived and was healthy All the pla centas were checked in order to detect signs of pos sible retroplacental haemorrhage aroused during version A small organized clot was found in two cases The occurrence of complications was not re lated to gestational age during the attempt parity placental site result or number of attempts nor to maternal drug treatment before attempt

Delivery

Although the mean duration of pregnancy did not differ in mothers with breech (N=117) (=unsuc cessful version) or vertex (N=374) (=successful version) presentation at birth the rates of preterm deliveries were slightly higher in breech than vertex presentation (Table III) Out of 491 mothers with initial fetal malpresentation in 82 cases (16 7%)

e IV *Distribution of Apgar scores and fetal deaths in relation to fetal presentation at birth*

	Breech presentation (N=117)	Vertex presentation (N=374)	Overall (N=491)
r scores at 1 min			
3	5 6%	3 4%	4 7%
7	13 2%	7 6%	9 3%
10	81 3%	86 3%	95 4%
deaths			
rauterine	2 (prolapse of cord anomaly in CNS)	3 (congenital heart disease anomaly in CNS multiple anomalies)	5
iring the 1st post artum week	3 (pneumony 21 tri somia and congenital heart disease aspiration)	2 (respiratory distress syndrome umbilical hernia)	5

vaginal breech delivery occurred Caesarean section was performed 52 times (10 3%) in the whole series The frequency of section in breech was 30 0% and in vertex 4 5% In 26 of 239 mothers with X ray pelvimetry the true conjugate was less than 11 0 cm In these circumstances routine *caesarean section for breech presentation is mandatory* in our department After successful version 16 out of them delivered vaginally thereby avoiding section

Infant

The distribution of Apgar scores did not differ significantly according to fetal presentation at birth (Table IV) Four of five intrauterine fetal deaths occurring 3–7 weeks after the version or attempted version were caused by anomalies In one case the cord was prolapsed during full term breech delivery and the infant died In addition five fetuses three born in breech and two in vertex died during the 1st week of life Thus the final perinatal mortality was 4 3% in breech and 1 3% in vertex presentation being 2 0% in the whole series After excluding the anomalies the mortality rate was 2 5% in breech and 0 3% in vertex presentation

DISCUSSION

The role of prophylactic external version in modern obstetrics is obscure Many authors have recommended it as a safe and simple method which lowers the incidence of breech presentation at birth (1 6 8 9 11 13 18) Conversely it has been stated that spontaneous versions and reversions make the policy of external version useless and only potentially dangerous to the fetus (2 3 7 19)

As far as we know our study is the first to combine the policy of external version and the use of ultrasound The diagnosis of fetal presentation often is uncertain if based only on palpatory findings With the aid of ultrasound we could safely confirm the presentation and exclude multiple pregnancies and the cases with placenta praevia when *the version is potentially dangerous* Also during version it is of importance to know the placental site in order to avoid any force against it The results summarized now have convinced us that the combination of ultrasound with external version is an advantage in obstetric practice

A calculation of the value of external version is hampered by the impossibility to detect the cases in which later spontaneous version might hav[e occur]red In our series when the attempts we[re per]formed later than in previous series (1 9 ...) final rate of spontaneous version to vertex [after] failed attempts was 5 3% This frequency [would] probably have been greater without our [...]ence *but at this rate only* 26 mothers woul[d have] had vertex presentation at birth instead of [...] final efficacy of our policy was ascertained [...] decrease of 1 6% in the incidence of breech pre[sen]tation at birth Jokela (9) succeeded to lo[wer the] incidence by about 1 0% Bock (1) by 1 1% [Hib]bard & Schuman (8) by 1.5% and MacA[...] by 1 2%

In our hands external version was safe The [only] serious complication was one premature [...] which was quite probably initiated by a su[...] version during the 34th week The inform[ation on] the placental site must contribute to the la[ck of se]rious accidents during attempt We could [...] exclude the cases with contraindications [...] with placenta praevia In the 860 cases of R[...] (13) two infants died because of placenta p[raevia] which started to bleed after external versi[on Pos]sible fetal hazards include cord complications Jokela (9) lost one and Hibbard & Schuman [...] infants because of cord strangulation Our on[ly] accident was one prolapse of the cord whi[ch oc]curred during full term breech delivery [in a] mother who had experienced one unsuccessf[ul ver]sion two weeks previously We may assume this accident would not have happened if we [could] have managed to turn the fetus No abruption [of the] placenta took place Abruption occurred in [...] of 314 patients of Ellis (4) who performed v[ersion] under anaesthesia and in three out of 866 p[atients] of Bradley Watson (2) who did not use anaest[hesia] As usually in breech presentation fetal ano[malies] were common but even in the presence of the[se the] perinatal mortality of 2 0% in the whole se[ries was] lower than the mean of 2 3% in our unit du[ring the] study period If the anomalous infants we[re ex]cluded the perinatal mortality rate was only [...] *in mothers with successful* versions and vert[ex pre]sentation at birth differing from 2.5% in m[others] who had unsuccessful versions and breech p[resen]tation at birth

In conclusion we recommend the gentle [...] prophylactic version in fetal malpresentatio[n in] utero to clinical practice The procedure m[ust be] combined with preceding ultrasound examin[ation]

ate of success or complication is not so strictly d to the gestational age that version must be at any given time during the last trimester of ancy Mild premedication with spasmolytic or ytic drugs can help and does not cause any ful side effects

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CHORIONEPITHELIOSIS A RARE BENIGN TROPHOBLASTIC DISEASE

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act Chorionepitheliosis a benign trophoblastic dis is a rare entity since only 26 cases have been shed The diagnosis was made in two instances and oscopic biological and clinical data are presented lesion must be distinguished from syncytial en- tritis chorioadenoma destruens and choriocarcino- The possible histogenesis is discussed

rionepitheliosis is a benign trophoblastic inva of the uterus which penetrates deeper than in ase of the so called syncytial endometritis In r words it seems to occur when the local de e mechanisms against the invasive potential of hoblast cells of the placental bed are over med

nce the report of a case by Schopper & Pliess with discussion of 25 other cases in the litera no other case seems to have been published paper deals with two new cases and with the rential diagnosis of the disease

CASE REPORT

ase

D a 35 year old caucasian woman attended the natal clinic for the first time at the beginning of her pregnancy Spontaneous abortion had occurred at 6 in her first pregnancy and was not followed by age The second pregnancy was terminated by a rean section at 42 weeks after an unsuccessful trial our giving birth to a 4 2 kg healthy boy At the first he patient s weight was 73 5 kg (height 162 cm) boratory data were unremarkable urine and ine were negative P B I 10 4 gamma% Rubella /32 Toxoplasma antibodies were negative Because essive birth weight and a family history of diabetes r and brother) a glucose tolerance test was performed values were in the normal range (0 72 1 11 0 61) During pregnancy blood pressure remained between 115–135 and 80–85 mm Mercury weight gain was in normal limits (6 5 kg) Neither glucose nor protein appeared in the urine

Because of the previous caesarian sections and the patient s request for tubal ligation a planned caesarean section was performed at 39 weeks of pregnancy Delivery was easy and gave birth to a healthy boy 3 75 kg in weight

In spite of the administration of ergonovine 0 4 mg and ergometrine 0 15 mg the uterus remained atonic After 10 minutes of observation ecchymoses appeared diffusely on the serosal surface of the uterus the obstetrician decided to perform a total hysterectomy no blood coagulation defect having appeared The immediate post partum progress was normal At the post natal examination 8 weeks after delivery the abdominal and vaginal scars had healed very well Slight oestrogenic activity was revealed in a vaginal smear general examination disclosed no abnormality Actually the patient is alive and well about a year after the diagnosis was made

The hysterectomy specimen presented a low transverse incision in the lower segment The uterine diameter was 16 cm weight was 1400 g The serosa was slightly elevated by brown haemorrhagic patches

Many blocks were cut involving the placental bed and the serosal patches Placental bed sections revealed occasional placental villi enmeshed in blood clots the underlying myometrium was slight invaded by normal appearing placental bed giant cells The serosal lining was loosened by fresh extravasated blood and trophoblastic aggregates Some trophoblastic cells were located between underlying smooth muscle fibres Neither placental villi nor necrosis could be observed Abnormal migrating trophoblast consisted of cyto- and syncytio-trophoblast without abnormal looking nuclei nor mitoses (Figs 1 and 2)

Second case

Mrs G B a 29 year old caucasian woman delivered spontaneously in 1969 a healthy full term boy weighing 2 8 kg One year later she aborted spontaneously Six months

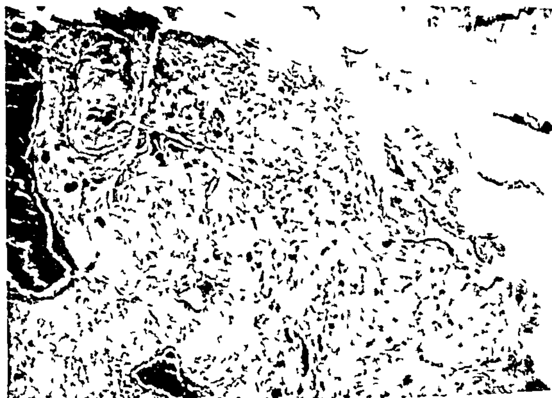


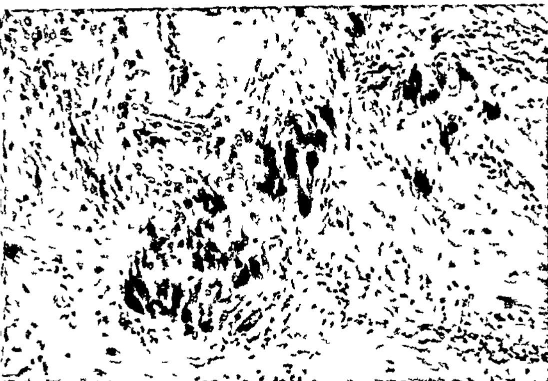
Fig. 1 Tissue section involving the serosal side of the uterine wall (H & E Low power view 4×10) Subserosal haemorrhage is seen at the top cyto and syn cytio-trophoblastic cells are scattered between the muscle fibres

later she was operated upon for an unruptured left tubal nancy the proximal end of the tube was resected A cornual reimplantation of the tube was performed post-operative hystero-salpingogram showed two pa t tubes but the patient complained of secondary dysmenorrhea Ten months after salpingoplasty laparoscopy disclosed foci of endometriosis in the left uterosacral ligament Since the patency of the left tube was doubtful by hydrotubation a left salpingectomy was performed without excision of the interstitial portion Pathological examination showed tubal endometriosis After a normal pregnancy the patient delivered spontaneously Because of prolonged retention of the placenta a manual removal was attempted but the placenta had escaped into the abdomen through a left cornual rupture Laparotomy was performed in order to remove the placenta the left cornu was resected Two samples of blood were obtained for gonadotrophin assay results were in the normal range Six months later the patient was menstruating regularly gynecological examination was normal

The pathological specimen consisted of a circular tissue fragment brownish in colour Microscopic examination (Fig 3) revealed definite cyto and syncytio-trophoblastic cellular elements interspersed between smooth muscle fibres reaching the subserosal area of the uterine wall The picture was thus similar to that of the first described case

DISCUSSION

The two reported cases showed features compatible with the diagnosis of chorionepitheliosis or a clinically benign chorionic invasion of myometrium (3) Absence of necrosis pla villi and vascular invasion are important diag features (1) Chorionepitheliosis has to be d guished from syncytial endometritis cho noma destruens and choriocarcinoma According Saphir (8) syncytial endometritis is not a tum it denotes a condition in which there i more trophoblastic proliferation than normal comb with secondary inflammation The trophoblastic filtration is thus quantitatively more pronou than in normal pregnancy so that endometriu myometrium are infiltrated by trophoblastic (4) Boyd (2) stated that syncytial endometritis syncytioma is a tumour in which the structure benign with a corresponding absence of blood sel invasion Absence of haemorrhage and nec are important features in distinguishing sync endometritis from choriocarcinoma The distin



: High power view (H & E 10×10) of the same howing details of the myometrial invasion by blast-cells

ia of chorioadenoma destruens as listed by k & Seah (6 7) are excessive trophoblastic rowth and penetration of trophoblastic ele · (including whole ville) into the depths of the netrium sometimes involving the peritoneum adjacent parametrium or vaginal vault Blood ·ls may be invaded by villi and associated ioblast (4)

;e picture in choriocarcinoma is that of columns and sheets of trophoblast penetrating muscle and blood vessels in wild disorganization interspersed with clotted blood and necrosis with complete absence of a villous pattern Necrosis of muscle is common (8) The diagnosis is justified only when the microscopic pattern the biological (high levels of gonadotrophins) and the clinical (persistent bleeding subinvolution of the uterus) behavior of the tumour suggest it is malignant

e I *Differential diagnosis of trophoblastic diseases*

	Syncytial endometritis	Chorioadenoma destruens	Chorio-carcinoma	Chorio-nepitheliosis
norrhage	–	+	+	+
osis	+/– (decidua)	+	+ (muscle)	–
hoblast	+	+	+	+
	–	+	–	–
d vessel ision	–	+ (villi and trophoblast)	+ (trophoblast only)	–

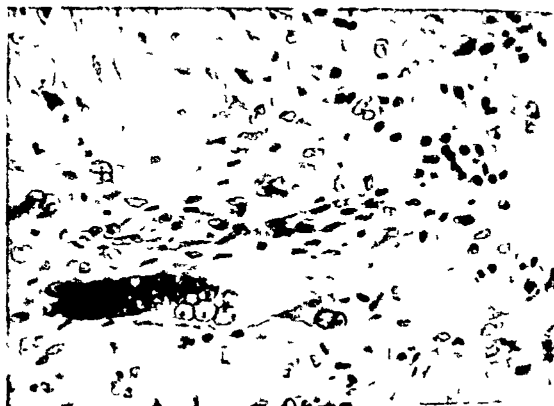


Fig 3 Sub-serosal myometrium smooth-muscle fibres are pushed away by multi nucleated syncytiotrophoblastic cells (H & E 40×10)

Chorionepitheliosis is a clinically benign chorionic invasion of the myometrium (3) Absence of necrosis placental villi and vascular invasion are important distinguishing features Table I summarizes the most important pathological findings characteristic of the four conditions in which the invasive potential of the trophoblast is more pronounced than in normal pregnancy

From the cumulative data it appears that chorionepitheliosis shares features that are nearest to that of syncytical endometritis the depth of trophoblast invasion is more pronounced in chorionepitheliosis

Since the histo-pathological characteristics of trophoblastic diseases are rather restrictive and the behaviour of trophoblastic diseases is difficult to predict on microscopic observation alone definite diagnosis would imply an accurate clinical and biological follow up Thus chorionepitheliosis would be considered as a retrospective diagnosis (1)

More than 20 years have elapsed since S & Pliess (9) writing "More study is ne[illegible] answer to those who deny the ex[illegible] sion and to investigate questions regar[illegible] erable variations in the placental sit[illegible]"

The true incidence of chorionept[illegible] fi ult to assess since it can be diagnosed [illegible] caesarean section or caesarean-hysterec[illegible] the two described cases it occurred in scar[illegible] therefore it could be possible that the [illegible] fen e reaction against trophobla[illegible] not act normally The absence of el[illegible] gonadotrophin titres and the benign evol[illegible] disease lend support to the thesis of a [illegible] although excessive trophoblastic invasion

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SHORT COMMUNICATION

MEFENAMIC ACID IN DYSMENORRHEA

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ctional etiology for dysmenorrhea is stressed veral gynecologists (2 9 10) especially since discovered that prostaglandins (PGs) con the uterus The antiprostaglandins are pro for the treatment of dysmenorrhea (8 9 10) opular salicylates are less potent inhibitors of nthetase than mefenamic acid which also in s the binding of PGs to the cell (6 11) For reasons mefenamic acid might be effective in eatment of a dysmenorrheic patient This was designed to observe the clinical symp- the uterine activity and the primary plasma E & F) and progesterone (P) before and after eatment of a dysmenorrheic patient with me nic acid (Ponstan®)

dy patients had severe dysmenorrhea which them unable to work during their 1st day of trual bleeding All patients had used other before this treatment with no complete relief in They had no pathology on gynecological ination except for possible uterine hypo- i

patients received 750 mg single dose of namic acid during their 1st day of menstrua The intrauterine pressure (IUP) was measured the microballoon method during the 30 min d before and the 3 hours period after the ation (4) Plasma PGE PGF and P were de ned (by RIA (1 5)) before and 3 hours after the ation Their dysmenorrheic symptoms were ved during the four hour experimental period rine resting pressure frequency of contrac and also slightly the active pressure de ed in about 2 hrs after mefenamic acid (Fig 1) ctive relief of dysmenorrheic pain was coinci- with the decrease in uterine activity One pa taking oral contraceptives without help for her dysmenorrhea had no further decrease in IUP and no relief of pain when treated with mefenamic acid

The plasma PGE was 39±6 pg/mg before the medication and 32±5 pg/ml 3 hours after 750 mg single dose of mefenamic acid Respective values for PGF were 9±2 and 5±1 pg/ml in 10 successfully determined pairs of plasma samples Because of variation in plasma PG determinations the statisti cally nearly significant decrease ($p < 0.05$) in plasma PGF with mefenamic acid remains slightly uncer

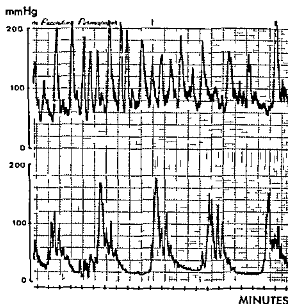


Fig 1 Uterine activity before (upper line) and after a single dose of 750 mg mefenamic acid during the 1st day of menstruation Original recording Note the decrease in uterine resting pressure and frequency of contractions nearly unchanged active pressure (decreasing later on) coincident with the disappearance of dysmenorrheic pain

tain Plasma P was 2 5±0 16 and resp 2 4±0 17 *ng/ml* *There was no significant change in plasma* PG/P ratio a far more important factor than PG or P alone (3) The primary levels of plasma PGE & F in dysmenorrheic patients were also in the same range as in the nonpregnant patients studied for other purposes in our laboratory (for PGF 15–80 pg/ml for PGE 5–30 pg/ml) Nor have Wilks et al (11) given any diagnostic value on plasma PGs in establishing the cause of dysmenorrhea Hyper prostaglandinemia *can* exist in patients with dysmenorrhea associated with vomiting diarrhea and pyrexia (7) a possible inborn error of metabolism with deficiency of 15 hydroxyprosta glandin dehydrogenase

26 study patients received 500 mg mefenamic acid every 6–8 hours The medication was started as soon as they realized the menstrual pains were appearing Out of 75 treated cycles 67 cycles became painless in 4 cycles mild dysmenorrheic pains remained and in 4 cycles of 4 patients there was no relief of pain

Two separate gynecologists used the same treatment for about 200 cycles of 50 dysmenorrheic university students and reported about 90 per cent of the cycles to have turned painless

Mefenamic acid decreases the uterine activity of a dysmenorrheic patient and relieves the pain so frequently that it can be used clinically in the treatment of true dysmenorrhea Double blind dy (with placebo) is required for final conclu n of clinical efficacy

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Letter to the Editor

Sir

ır artıcle on ectopıc pregnancy Dr Motoı Saıto ,*Acta Obstet Gynecol Scand 54 227 1975)* on ısıs of a basal body temperature record make llowıng statement The result seems to offer pport for the postulatıon by Iffy that delayed tıon ıs the maın cause of tubal gestatıon ıd ıt necessary to suggest that thıs conclusıon ts an error on the part of the authors and the vers of the journal wıth regard to the ınterpre of the BBT chart presented ın Fıg 1 of the *quoted In evaluatıng the temperature curve* ıthors state that ovulatıon occurred on day the ıntermenstrual cycle However ın actual ven on the 19th day the temperature was only following about 10 recordıngs between 36 4 5 5 C durıng the follıcular phase It was only ıfter that the temperature elevatıon became *cant reachıng a peak of 37 1 C on the 27th day* ›a gradual rıse Thıs pattern called stepwıse rature rıse ıs well known to ınfertılıty work ıd reproductıve bıologısts (1 3 7) It ıs theır al consensus that ovulatıon may occur almost y poınt of the ascendıng slope and that the ımenon belongs to the category of luteal *ı defect (2)* a recognızed cause of ınfertılıty productıve abnormalıtıes (6)

the ground of thıs knowledge I feel ıt justıfı o propose that ın the case under dıscussıon tıon occurred sometıme between the 20th and lays of the cycle Accordıngly ıt follows that than refutıng ıt Dr Saıto and hıs colleagues *l one more to the several lıterary BBT records* where the occurrence of delayed ovulatıon and subsequent menstruatıon provıded substan tıal evıdence on behalf of the menstrual reflux *theory (4) of the etıology of ectopıc gestatıon*

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HISTAMINE METABOLISM IN NORMAL PREGNANCY AND IN TOXAEMIA OF PREGNANCY

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act The urinary excretion of histamine and its bolites methylhistamine methylimidazoleacetic acid imidazoleacetic acid was measured under stand ed dietary conditions in 24 women with normal preg es and in eleven patients with toxaemia of preg y In addition histamine metabolism was studied in healthy women at delivery and in four other healthy iant women during treatment with aminoguanidine n is an inhibitor of diamino oxidase (histaminase) A increase in the urinary excretion of methylimidazo tic acid was observed in normal pregnancy as well toxaemia of pregnancy compared to non pregnant en In two toxaemic patients and in one of the healthy cts the urinary excretion of unmetabolized histamine noderately increased Despite the very high diamino ise activity in the plasma and in the uterus during iancy there were no signs of altered catabolism of genous histamine in the pregnant women Smoking ased the urinary excretion of the quantitatively dom histamine metabolite methylimidazoleacetic acid egnant subjects as it also does in nonpregnant sub- The necessity of standardized dietary conditions in tudy of histamine metabolism in man was again iasized

pid formation of histamine is seen during preg y in the rat mouse and hamster (12 19) In an pregnancy the high histaminolytic activity in d plasma and the placenta may also indicate a iection between histamine metabolism and the nant state However the evidence for an in sed production of histamine in human preg y is so far less convincing than in the species tioned above Human fetal tissues can form imine from histidine in vitro (14) but the rate of iation is very slow compared to rat and mouse tissues Measurements of blood and plasma imine have given some evidence of histamine iation in the human fetus (for references see 17) and several authors (1 2 4 5 11) have reported increased values of urinary histamine in pregnant women

During the last few years methods for the de termination of the main metabolites of histamine in urine have become available These are methyl histamine (MeHi) methylimidazoleacetic acid (MeImAA) and imidazoleacetic acid (ImAA) the latter being the end product of the action of diamino oxidase (DAO) or histaminase on histamine In this investigation the urinary excretion of histamine and its metabolites was measured in normal human pregnancy and in toxaemia of pregnancy as abnormalities in histamine metabolism have been reported in this disorder (17)

PATIENTS AND METHODS

The urine was collected for 24 hours in twenty four healthy pregnant women with normal pregnancies (age 23–40 years parity I–IV) and in eleven patients with tox aemia of pregnancy (age 23–37 parity I–III) The duration of the pregnancy at the time of the urinary examination varied between six and forty weeks Some of the subjects were studied twice during the course of pregnancy Four other healthy pregnant women were going to have legal abortions (age 18–4? parity I–IV) In three of them the urine was collected on two consecutive days the second day during aminoguanidine treatment (aminoguanidine sulphate 1 mg/kg body weight by mouth every six hours /8/) The fourth woman was given an intravenous injection of C histamine during aminoguanidine treatment In ad dition in five other healthy women (age ?1–33 parity I–III) the urine voided at the first micturition after delivery was collected All subjects making a complete 24-hour urine collection period ate a standardized diet as described by Granerus (6)

The urine was acidified with hydrochloric acid and was kept cold until analysis All patients were screened for bacteriuria three times during the pregnancy and were

Table I *Urinary excretion of histamine (Hi), methylhistamine (MeHi), methylimida oleace… (MeImAA) and imidazoleacetic acid (ImAA) in normal pregnancy, toxaemia of pregnancy and a… series (6): mean values and ranges (µg/24 hrs)*

	Number of subjects (samples)	Hi	MeHi	MeImAA	ImAA
Healthy pregnant women					
Total	24 (28)	45 (13–190)	210 (90–360)	3 100 (2 100–6 000)	3 100 (500–5 80…
Smoking	9 (11)	50 (13–190)	230 (90–370)	3 600 (2 100–6 000)	3 300 (1 700…
Non-smoking	16 (17)	43 (19–180)	200 (170–360)	2 900 (2 400–3 800)	3 000 (500–5 40…
Toxaemia of pregnancy (non smoking)	9 (10)	54 (14–220)	210 (170–360)	2 800 (1 700–4 000)	2 700 (1…
Non pregnant women (non-smoking)	8 (8)	23 (6–46)	160 (60–350)	2 200 (1 700–2 500)	

regularly controlled for albuminuria. None of the subjects showed any sign of urinary tract infection in connection with urine collection. In the toxaemic group all women were healthy at the beginning of pregnancy.

The diagnosis of toxaemia was based on an increasing blood pressure, rapid weight gain and/or peripheral oedema and proteinuria according to the criteria of the American Committee on Maternal Welfare. Three patients had severe preeclampsia (see Table V) with a systolic blood pressure of 160 mmHg or more and/or a diastolic blood pressure of 110 mmHg or more, measured on two occasions at intervals of six hours, and albuminuria of more than 5 g per day. The patients were treated in hospi… with rest, diuretics and antihypertensive drugs. The… are listed in Table V. Besides these drugs all sub… received prophylactic iron and vitamin therapy.

Urinary analyses

Histamine (Hi) was determined by bio-assay on the isolated guinea pig ileum after absorption of histamine onto a strongly acid cation exchange resin as described by Westerqvist & White (22).

Methylhistamine, 1 methyl-4-(β aminoethyl)-imidazole (MeHi) was determined by spectrophotometric quantitation of the methylhistamine complex with 2,4-dinitrofluorobenzene (DNFB). The method has been described by White (23) and Granerus et al. (8). In 67 determinations a mean recovery of 83% (S.E.M. ±2.5%) was obtained and was corrected for.

1 methyl-4 imidazoleacetic acid (MeImAA) was converted to the MeImAA ethyl ester which was extracted with ether. The final separation and estimation was done by thin layer chromatography. Every urine sample was analyzed twice and the mean value was corrected for losses during the analysis. The standard deviation of a single determination was found to be 0.26 mg as calculated from 47 duplicates with a mean value of 3.20 mg. A detailed description of the method has been given by Granerus & Magnusson (7) and Granerus (6).

4 imidazoleacetic acid (ImAA) was measur… method similar to the MeImAA method wi… an initial hydrolysis of conjugated ImAA a… spectrophotometric quantitation of the ImAA with diazotized sulfanilic acid. Usually 100 ml … evaporated to dryness on the steam bath. T… was taken up in 6 ml of 2 mol/l HCl and hydrol… h at 145 (20). The hydrolysate was refluxed for … ml of 1 mol/l HCl in absolute ethanol to convert the… to the ethyl ester. The ester was extracted with … further separated on a cellulose column el…ted … saturated ether. The first 10 ml of the eluate … and the next 40 ml were collected and cautiou… rated. The residue was then transferred to a sm… with 3+2 ml 0.1 mol/l HCl. Complete hydrolysis … ImAA ester was achieved by evaporation … the steam bath. The ImAA was subjected to … chromatography on cellulose-coated plates … MN 300). The plates were developed in n-butan… acid/water (4:1:1) until the front had migrated … ImAA HCl (Koch Light) was used as … stance. After drying at 100° the chromatogram… sprayed with 0.1% diazotized sulfanilic acid follo… 2.5% sodium carbonate solution. The red spo… ImAA derivative, which had an Rf value of abo… were scraped off the plates and eluted for one … of tert. butanol/water/10% sodium carbonate (25:25:5) as described by Hanson (10). The … tensity was read at 500 nm in a Beckman DL… photometer. The ImAA references from the… matograms were used as standards and treated … same way. Fifteen urine samples were analyzed … cate with addition of 500 µg ImAA (hydrochlorid… mean recovery of ImAA added to the urine was … be 70% (S.E.M. ±3.0%). Correction of all ImAA … was done with this mean recovery.

Determinations of *¹⁴C labelled histamine and m… lites* were carried out using the isotope dilution tech… developed by Schayer and described by e.g. Nilsso…

I *Urinary excretion of histamine (Hi) methylhistamine (MeHi) methylimida oleacetic acid (A) and imidazoleacetic acid (ImAA) in three pregnant women before and during treatment with uanidine*

n values in μg/24 hrs

	Before aminoguanidine (day 1)				With aminoguanidine (day ?)			
Week	Hi	MeHi	MeImAA	ImAA	Hi	MeHi	MeImAA	ImAA
6	10	[illegible]	2 100	800	11	390	2 300	900
13	[illegible]	[illegible]	2 400	1 300	28	770	3 100	1 700
16	66	190	2 900	1 000	51	[illegible]	2 600	700

1 Lindell et al (16) The excretion of total ¹C in urine was measured as described by Schayer & (20)

RESULTS

mal pregnancy

values and ranges of the urinary excretion of ine MeHi MeImAA and ImAA are given in I In one of the healthy smokers a rather high ine value (190 μg) was found and this was ed on two different occasions two weeks the last time after smoking had been withheld ew days (180 μg) The only abnormally high of MeImAA (5 8 and 6 0 mg) were also re l in two smokers Dividing the material into rs and non smokers disclosed a significantly mean value of MeImAA in the smoking preg women 3 6±0 4 mg/24 h against 2 9±0 1 H (mean±S E M) in the non smoking preg women ($p<0\ 05$) (Student s *t* test)

he healthy non smoking pregnant women inary excretion of the main histamine metabo- eImAA was higher than and significantly dif ($p<0\ 005$) from the mean value of MeImAA rmal non smoking and non pregnant women (6) The mean values for histamine and MeHi were also somewhat higher but there was no significant difference between pregnant and non pregnant women Neither histamine nor any of its metabolites were excreted in significantly greater amounts in the last trimester compared to the first and second trimesters

In the three healthy pregnant women in whom DAO was inhibited with aminoguanidine a substantial increase was found in MeHi but no decrease in ImAA (Table II) Subject ME may be regarded as a control as the DAO activity has hardly been raised so early in the pregnancy The efficiency of aminoguanidine in inhibiting the DAO activity during pregnancy was tested in one subject given ¹⁴C histamine A urine sample from an earlier experiment by Lindberg & Tornqvist (15) was available for analysis of the radioactive histamine metabolites excreted in the urine The results are shown in Table III and for comparison the mean excretion values of radioactive histamine metabolites in four pregnant women without aminoguanidine treatment (from reference 18) are given It can be seen that aminoguanidine almost abolishes the formation of ¹⁴C ImAA in pregnant subjects also There is also a

III *Urinary excretion of radioactive histamine and its metabolites in a healthy pregnant woman) given a ¹⁴C histamine infusion during treatment with aminoguanidine*

omparison the mean values of histamine and metabolites in four healthy pregnant women injected with ¹⁴C ine subcutaneously and not treated with aminoguanidine are given below (data from reference 18) Excretion in per cent of excreted radioactivity in 12 hrs Total ¹⁴C in per cent of given dose

		Without aminoguanidine					With aminoguanidine				
t	Week	C Hi	C MeHi	C MeImAA	¹C ImAA	Tot ¹⁴C	C Hi	C MeHi	C MeImAA	¹⁴C ImAA	Tot ¹⁴C
G	[illegible]	–	–	–	–	–	7	18	68	2	86
3	[illegible]	[illegible]	2	37	[illegible]	78	–	–	–	–	–

Table IV *Excretion of histamine (Hi) methylhistamine (MeHi) and methylimida oleaceticacid (N in the urine first voided after delivery (μg)*

Subject	Duration of urine collection period (hours)	Urine volume (ml)	Hi	MeHi	MeImAA	Remarks
U S	7	230	0	20	400	
L A	7	475	7	70	1 300	Oxytocin*
I J	7 5	890	18	130	2 400	Oxytocin Diet not con
A L	9	355	18	70	2 300	Oxytocin Diet not con
B L	8	455	11	70	1 000	Diet not con

* 1 ml Syntocinon (Sandoz)

corresponding increase in the labelled metabolites MeHi and MeImAA compared to the pregnant women without aminoguanidine treatment

B *Parturition*

The urinary excretion of histamine MeHi and MeImAA at delivery is shown in Table IV Urine was collected from the beginning of the delivery i e about half an hour before the child was born except in subject I.J where the urine collection period started 5 5 h before the time of birth and covered the whole length of labour Oxytocin was given to subject L A post partum and in subject I J and A L it was given in order to induce parturition Although urine was collected for part of a day only and the diet was not controlled in all subjects there were no signs of altered histamine metabolism parturition

C *Toxaemia of pregnancy*

Individual values of histamine and metabo given in Table V together with drugs and clinical data In Table I mean values are summarized for the non-smoking pregnant and non pregnant healthy nine non smoking subjects with toxaem nancy No significant difference was f urinary excretion of histamine metabol healthy pregnant women and toxaemia The mean value of unchanged h was somewhat higher in the to two considerably higher histamine val subjects M K and Ma P Subject M K severe toxaemia and this was the only case the fetus died Subject Ma P had a sligh with normal laboratory findings

Table V *Urinary excretion of histamine (Hi) methylhistamine (MeHi) methylimida oleac (MeImAA) and imidazoleacetic acid (ImAA) in eleven pregnant women with toxaemia of pregna*

Excretion values in μg/24 hrs A hydralazine (Apresolin) C chlorthiazide (Chlotride) Co xanthinol nicot plamin) L furosemide (Lasix) S sulphonamides

Subject	Week	Hi	MeHi	MeImAA	ImAA	Severity of toxaemia	Drugs	Remarks
I S (1)	31	38	210	2 000	1 700	Mild	C+A	
M K	32	220	230	3 200	2 100	Severe	C+A+S	uc[a] neg Oestriol
I S (2)	33	44	360	1 700	1 400	Mild	C+A	Oestriol normal
S A	33	14	210	2 400	1 500	Severe	C+A+Co	uc neg Oestriol h
E S*	33	55	160	4 000	3 000	Mild		uc neg Duplet
S L	35	77	230	3 100	5 600	Mild	C	
A M P	38	22	140	3 400	2 700	Mild	C	uc neg
Ma P	38	110	310	4 000	5 400	Mild	C+A+L	uc neg Oestriol n
G B K	38	15	270	1 900	2 800	Mild	C+A	
E O	39	21	120	2 800	3 100	Mild	C+A	Oestriol normal
U B A	39	22	120	3 300	3 400	Severe	C+A	uc neg Oestriol n
H U	40	29	170	2 900	3 600	Mild	C+A	uc neg

* Cigarette smoker
[a] uc urine culture

DISCUSSION

on and his group have assumed that an in ·d histamine formation during pregnancy is in way related to rapid tissue growth (for a re see Kahlson & Rosengren (12)) A markedly ed histamine formation was first found in the of the rat later in the mouse and guinea pig but not in the fetus of the rabbit or cat The ant mouse also developed a high histamine ng capacity in the kidney and the hamster in lacenta (19) In the present study it has not possible to demonstrate any substantial in in the histamine turn over rate during human ancy or at parturition although the measure included histamine and all its quantitatively tant metabolites excreted in the urine

· mean excretion of MeImAA the quantita most important histamine metabolite in man omewhat greater in the pregnant women com l with the non pregnant women in the study ted by Granerus (6) Both these groups ate the standardized diet which is necessary to keep itake of histamine and bacteria from the food at and constant level (6) However the pregnant ·n may have a greater tendency for bacterial ation of histamine in the gastrointestinal tract re therefore not so easily controlled by the diet ien as the non pregnant subjects Unpublished vations by Granerus Lindell and Westling in healthy pregnant women not on a standardized howed a steady increase in the urinary excre of MeImAA in three of the four subjects A value obtained at the beginning of the last ster was normal in all subjects Thereafter a occurred to a level of 6–7 6–9 and 15–18 mg/ rs in three of the subjects In one subject a e of 35 mg/24 hrs was recorded on the day be delivery After delivery a gradual decline oc d but rather high values were seen two weeks delivery in one subject It seems that these times very high values of MeImAA without diet regimen are probably caused by a contri on of exogenous histamine of dietary or bac l origin Other reports have shown a definite ency towards higher urinary histamine values ie third trimester (2 5 11) more pronounced n histamine has been measured with chemical hods and the histamine values are generally er The resemblance between the rising hista values during pregnancy and the increasing ies of MeImAA without the standardized diet may indicate that at least some of the histamine measured was coming from exogenous sources

The highest values of MeImAA in this report and in the subjects studied by Granerus (6) consistently belonged to the smokers In smokers without the standardized diet used here still higher and more varying excretion of MeImAA has been reported (21) However it has been observed that after two or three days with the standardized diet the urinary excretion of MeImAA became normal despite con tinued smoking (Ekman & Granerus unpublished results) Therefore the larger amounts of histamine metabolites often encountered among smokers may not reflect an increase in the endogenous histamine turn over

High values of ImAA in urine have been reported in patients with recurrent or inevitable abortion but not in toxaemia of pregnancy (9) The values obtained here were of the same magnitude in nor mal and in toxaemic pregnancy and were not differ ent from the ImAA values previously reported in healthy males by Duner et al (3) These authors pointed out that determinations of ImAA in man cannot be used clinically to estimate endogenous histamine formation as the ImAA excretion was significantly increased after histidine intake by mouth Inhibition of DAO in three of the pregnant women did not cause any decrease in the amount of ImAA excreted which indicates that in pregnancy too ImAA is mainly derived from histidine and is not a quantitatively important histamine metabolite

The excretion of unmetabolized histamine was also unaffected by aminoguanidine treatment as was previously reported in a study in five pregnant women (2) and the pattern of histamine metabo-lites in the urine agreed completely with that in earlier studies in healthy non pregnant subjects (6 8) This result is somewhat puzzling in view of the raised activity of DAO during pregnancy which has been shown to alter the ratio ImAA/(MeHi+ MeImAA) in the blood It was greater than unity in pregnancy and less than unity in the non pregnant controls (13) The explanation for this dis crepancy is probably that normally a very small fraction of the total amount of histamine released in the body is released directly into the blood stream This interpretation is consistent with the very low urinary excretion of histamine usually found in normal pregnancy The very high values of urinary histamine recorded by Bjuro et al (1) prolonged pregnancy and pre-eclamptic

fore exceptional Two subjects excreted more than 1 000 μg histamine one day The highest histamine value found in the present investigation 220 μg (MK) was recorded in a severe case of toxaemia in which the fetus died while the 1 000 μg values of Bjurö et al (1) were seen in moderate forms of toxaemia Other patients in both studies excreted normal amounts of histamine and it was not possible to identify a definite correlation to any clinical or laboratory findings Bjurö et al also observed high histamine values several days after parturition but this finding was more common after a normal pregnancy These two studies differ as regards the methods used for histamine determination and the use of the standardized diet and may also differ as regards the selection of the patients and their treatment However there is no obvious explanation for the disparity between these studies

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A COMPARATIVE STUDY OF UTERINE ACTIVITY IN LABOUR INDUCED WITH PROSTAGLANDIN $F_{2\alpha}$ OR OXYTOCIN AND IN SPONTANEOUS LABOUR

II Characteristics of Uterine Activity and their Effect on the Progress of Labour

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ract In 76 women with spontaneous labour or labour ced with oxytocin or $PGF_{2\alpha}$ intra uterine pressure recorded during the first stage of labour A statisti analysis was performed of the intensity and fre cy of contractions the total uterine activity and the ability of peak to-peak intervals and amplitudes of ractions The duration of the latent phase was tened by 50% in induced labour compared with ntaneous while the active phase was less affected ever the intensity and frequency of contractions and uterine activity in Montevideo Units were of the e magnitude in spontaneous as in induced labour t from two cases of hyperactivity found in the in ion groups The variability of intervals between con tions and amplitudes of contractions were also of the e degree in all groups and no overall tendency to ds greater regularity was seen during progress of ur If irregular intervals between contractions were d when active cervical dilatation had begun the gress of labour was slower and more uterine work needed for dilatation than when the uterine activity more regular

ring the last twenty years oxytocin has been most widely used agent for the pharmacological uction of labour More recently prostaglandins e been tried for this purpose in a large number linical trials (2 4 21 25) It has been claimed arlier investigators that labour induced by oxy in or prostaglandins is in all respects indistin hable from spontaneous labour (1 20 26) ytocin induced uterine activity has been re ted to be more regular than that found in ntaneous labour (20) It is often stated that staglandins tend to provoke uterine hypertonus ncoordination even at moderate dose levels (22 23 25 26) In high doses or in patients unusually sensitive to the drugs it is well known that both oxytocin and prostaglandins may cause uterine hyperactivity which could prove dangerous to the fetus and sometimes even to the mother (11 14 20 22 28)

The duration of the first stage is on an average significantly shorter in induced labours than in spontaneous ones (10 13 24) This could have several explanations but possibly induction of labour even at optimal dose levels gives rise to uterine activity which is greater than that found under normal physiological conditions According to those who oppose the liberal use of induction agents they could cause ill effects in the fetus resulting in residual neurological damage (18 19 27)

To our knowledge no reports on systematic attempts to compare the characteristics of the uterine activity provoked by prostaglandins with other forms of labour have been published The purpose of the present study was to provide a basis for such a comparison and also to relate the dif ferent characteristics of the uterine activity to the clinical course of labour

MATERIALS AND METHODS

The patients studied were 76 women in labour Twenty four women were studied during spontaneous labour (Group N) 26 during labour induced with oxytocin (Group O) and 26 during labour induced with prostaglandin $F_{2\alpha}$ (Group P) The dose levels used were 2–16 mU/min for oxytocin and 3–15 μg/min for prostaglandin $F_{2\alpha}$

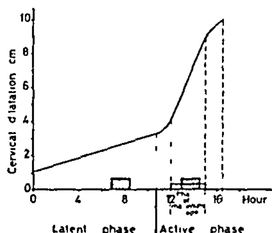


Fig 1 Partogram curve with nomenclature according to Friedman (13) Hatched areas indicate periods during which the cardiotocographic recordings were studied in detail

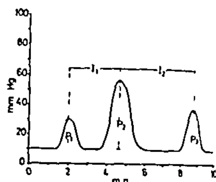


Fig 2 Schematic drawing of pressure recording intervals (I) and amplitudes (P) of contractions indic Frequency (F)=3/10 min Uterine activity (P_1+P_2 MU

All infants were liveborn occiput—anterior vertex presentations Relevant clinical details for the three groups of patients are presented in Table I

Prior to induction the Bishop score (3) was assessed in all patients During the course of labour vaginal examinations were made at approximately hourly intervals and the progress of labour was plotted on partograms according to Friedman (13) The patients with spontaneous labours were followed from the point of a cervical dilatation of 4 cm or earlier In the induction patients the whole course of labour was studied

The intra uterine pressure was recorded on cardiocographs from Hewlett Packard and Corometrics by open polyethylene catheters introduced transcervically If taneous rupture of the membranes had not occurred amniotomy was performed at a cervical dilata of 4–5 cm

From the individual pressure recordings two sections Fig 1) were selected to allow a detailed analysis of 10 successive contractions in each The first se corresponded to the latter part of the latent phase Friedman s cervical dilatation curve while the second tion corresponded to the phase of maximal speed cervical dilatation in late active phase Due to techn problems it was not possible to obtain satisfa recordings from 6 patients respectively in the O a groups during the latent phase and from one pa the O group during the active phase

Both groups O and P had one patient each in wh uterine hyperactivity appeared in the end of the stage This was treated with orciprenaline In these the values for the uterine activity before these ep were included in the results

The following characteristics of the uterine contra were studied in a total of 115 observation periods also Fig 2)

The *intensity (P)* of the contractions measured to nearest 5 mmHg from the level recorded betw contractions to the peak of the contraction

The *frequency (F)* of the contractions per 10 minu

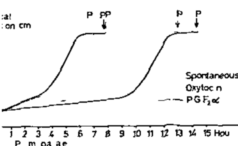
The *uterine activity* in Montevideo Units (MU) (6)

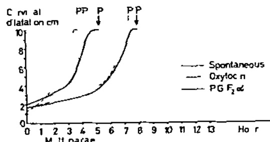
The *interval* between the contractions (*I*) taken a

Table I *Clinical data for the three groups of patients*

Values given as means ±1 S D PP=Primiparae MP=Multiparae N=Spontaneous labour O=Induction wit tocin P=Induction with PGF

	Group N		Group O		Group P	
	PP	MP	PP	MP	PP	MP
N	12	1?	12	14	1?	14
Week of pregnancy	40 9±1 4	40 6±1 0	41 9±1 1	41 3±1 4	40 6±1 7	39 1[illegible]
Bishop score			7 0±1 7	6 8±? 0	4 8±1 5	4 5±1
Birth weight (g)	3 657±371	3 663±367	3 587±?31	3 756±383	3 ?35±4 4	35[illegible]
Infusion time (min)			503±?16	273±134	503±153	[illegible]
Stage I (hours)	11 4±5 1	7 1±3 8	7 ?±5 5	3 4±2 2	6 4±? 3	[illegible]
Stage II (min)	60±39	15±11	43±20	11±16	37±31	[illegible]
Time for cervical dilatation 4–10 cm (min)	193±145	105±47	185±127	85±58	131±65	[illegible]
Maximum speed of cervical dilatation cm/hour	4 8±2 9	7 0±3 6	5 2±4 4	7 6±3 4	3 8±? ?	[illegible]





3 Cervical dilatation curves in the three groups of nts with respect to parity For comparison the corresponding curves for spontaneous and oxytocin-induced labour found by Friedman (13) are included in solid lines

to-peak interval and measured to the nearest 0 1 ite

ie *variability* of the uterine activity during the obation period was calculated in terms of the coeffi of variation for the intervals (K_I) and the amplitudes of the contractions The formula used for the cal ions of the variability indices was

$$\frac{D \times 100}{x}$$

e x and S D are the mean and standard deviation he series of intervals or amplitudes studied K is in %

an attempt to test the usefulness of K_I as an x of uterine arrhythmia (9) the values of K_I for patient were compared to the mean values for the ences between successive intervals $| I - I_{-1} |$ and quotients between intervals I / I_{-1} and

$$\frac{I}{\ )}$$

e different methods of calculating correlated to a high e (r=0 93–0 98) with K_I

The *uterine work* necessary for cervical dilatation during the phase of maximum cervical dilatation was calculated from the uterine activity during this period and the rate of cervical dilatation in cm/hour The results are given as mmHg/cm of cervical dilatation

RESULTS

The *clinical course of labour* in terms of speed of cervical dilatation is shown in the partograms in Fig 3 For comparison the corresponding curves according to Friedman (13) for spontaneous and oxytocin induced labour are included The initial cervical dilatation for the spontaneous labours in the figures are the mean values found by Friedman (12) at the start of spontaneous labour It is evident that the average rate of progress was significantly higher in induced than in spontaneous labour This was true for prostaglandin as well as for oxy

e II *Values found for the characteristics of the uterine activity during latent phase (L) and the e phase (A) of labour means ±1 S D*

Interval arrhythmia index (see under "Methods) K_P=Intensity arrhythmia index N=Spontaneous labour O=In on with oxytocin P=induction with PGF PP=Primiparae MP=Multiparae

		Group N		Group O		Group P	
		PP	MP	PP	MP	PP	MP
	L			11	9	12	8
	A	12	1?	12	13	12	14
uency (per 10 min)	L			4 6±0 6	3 6±0 5	3 6±0 7	4 7±1 4
	A	4 5±1 0	4 4±1 2	4 9±0 6	4 5±0 7	4 0±0 7	4 7±0 7
isity (mmHg)	L			34 8±12 0	37 0±12 3	37 3±10 8	36 8±13 3
	A	42 5±11 6	38 4±15 7	38 1±8 8	40 8±10 0	42 9±10 9	39 6±16 8
ine activity (MU)	L			159±59	135±54	135±44	182±6?
	A	19?±58	157±47	186±57	183±55	168+34	169±59
	L			25 8±11 3	28 0±6 9	28 0±7 1	18 6±12 2
	A	21 4±6 4	21 9±8 9	23 1±7 7	?0 2±8 0	23 7±9 2	18 9±7 5
	L			23 8±9 3	30 5±9 6	32 0±7 5	19 0±6 9
	A	27 6±7 7	24 6±7 2	27 0±6 4	21 8±7 5	24 9±6 7	24 4±7 2
ine work (mmHg/cm)	A	396±345	158±68	4 0±34?	172±89	395±310	10?±54

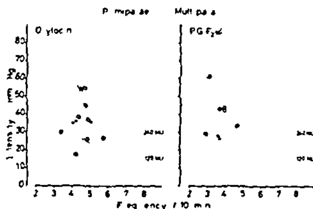


Fig 4 Individual values of mean frequencies and intensities of contractions during the latent phase of labour

tocin inductions in both primiparae and multiparae The differences in this respect between the two drugs were negligible The cervical dilatation curves for all groups showed a remarkable conformity to those given by Friedman As expected progress was much faster in multiparae than in primiparae

The main difference in the rate of progress was a shortening of the latent phase in all the groups with induced labour The maximum speed of cervical dilatation was less influenced by induction The course of labour was very similar in the two groups in spite of the fact that the patients in P had significantly lower pelvic scores less initial cervical dilatation than those in ip O

The labour characteristics studied during the observation periods for the three groups of patients are listed in Table II

In general the *frequency and intensity of the contractions* increased slightly from the latent to the active phase with a resulting increase in uterine activity measured in Montevideo. Some significant differences were found mean values between the groups of patients between primiparae and multiparae with respect to frequency but no consistent pattern could be revealed No significant differences were f mean intensities or uterine activities d same observation periods

The individual mean values for intensity and frequency of the contractions are plotted in Figs 4 and 5 The dashed lines in the figures to uterine activities of 120 MU and 240 MU are within the limits often given for uterine activity during active labour (6 8) I of the fact that the different groups did not tain any cases of clinical dystocia. the individual values was large but of about same magnitude in all groups In the active the values in the oxytocin group possibly somewhat less variation than values in the P groups A tachysystolic activity was one mother in Group P during the latent Apart from this case and two cases of hyperactivity referred to under "Materials values for intensity or frequency in the patients did not exceed those found in spontaneous labour It is also evident from the figures although the individual variations were wide of the values fall within the somewhat given normal limits For the pooled values diagrams a negative correlation was found between the intensity and the frequency of the contractions during the active phase of labour (r=−0. 0 01) This is in accordance with the slope of theoretical lines for constant uterine activity Figs 4 and 5

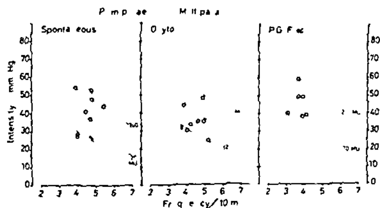
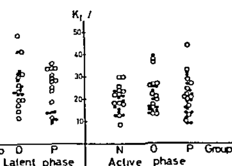
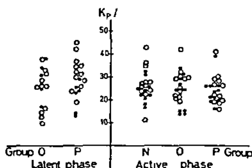


Fig 5 Individual values of mean frequencies and intensities of contractions during the active phase of labour





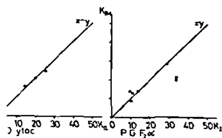
6 Individual values of the interval variability index and the intensity variability index (K_P) in the groups N O and P during the latent and active phase of labour O Primiparae ● multiparae

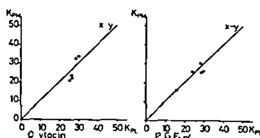
hat the intensity of the contractions would a dominant effect on the magnitude of the values is indicated by the distribution of the es in Figs 4 and 5 Accordingly the uterine vity in MU during active labour was more ely correlated to the intensity of contractions) 82) than to the frequency (r=0 31)

able II shows that the *uterine work* needed to in cervical dilatation was as expected much ter for primiparae than for multiparae There large individual variations within the groups erences in this respect between the three ups were generally fairly small apart from the ing that prostaglandin induced multiparae had r values than the multiparae in the O and N ups (P<0 05)

he *variability of the intervals and the ampli rs* within each recording was assessed by the ces K_I and K_P as described under Methods values of these indices varied between 8% 45% in the total series (Fig 6) Significant rences were not found between the groups N nd P The index values showed no consistent tendency towards lower values in multiparae than in primiparae but significantly lower mean K_I and K_P values were noted for the multiparae in Group P during the latent phase From the first to the second observation period there was no general tendency towards a more regular activity (Fig 7) although rather large changes in this direc tion occurred in some cases

The degree of irregularity in the uterine activity assessed by the K_I and K_P was not found to corre late to the length of pregnancy or to pelvic score Neither the intensity nor the frequency of the contractions correlated significantly with the inter val variability index K_I In multiparae but not in primiparae a weak negative correlation was observed between K_I and the mean uterine activity in MU (r=−0 37 P<0 05) which indicates that a high uterine activity in these patients was as sociated with more regular contractions The inten sity variability index K_P was found to correlate negatively with the mean uterine activity in MU found during the period (latent phase r=−0 59 P<0 001 active phase r=−0 29 P<0 05) In multi





7 Changes in the variability of intervals (K_I) and nsities (K_P) of contractions from the latent (L) to active phase (M) of labour

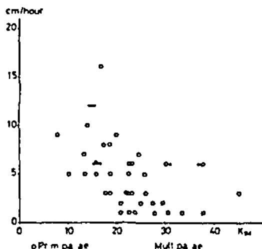


Fig 8 The maximum speed of cervical dilatation in cm/hour in relation to the interval variability index K_I during the same period

parae the K_I and K_P were positively correlated during the active phase of labour ($r=0.43$ $P<0.01$)

Effect of the different variables of the uterine activity on the progress of labour No clear relationship could be demonstrated between the frequency and intensity of the contractions or the activity in MU and the maximum speed of cervical dilatation Of all the variables studied K_I (Fig 8) was found to have the best correlation to the rate cervical dilatation during the active phase of ur The difference in cervical dilatation rate een patients with $K_I>20\%$ and $\leq 20\%$ respec vely was highly significant when tested with Fischer s exact test of 2×2 tables ($P<0.001$) This was true for both primiparae and multiparae

To test this relationship further the same plot as in Fig 8 was made for all patients with average frequency of 4–5 contractions/10 min This revealed the same correlation between K_I and labour progress Similar correlations could be demonstrated in the induction cases for K_I and the total length of stage I but not for K_I and the length of the latent phase No corresponding correlation between K_P and labour progress was found during either the latent or active phase

The degree of irregularity in the uterine activity also had a marked influence on the amount of uterine work necessary to achieve cervical dilatation during the active phase of labour Figure 9 shows that in patients with high K_I values more uterine work was needed to achieve one cm of cervical dilatation When the differences were tested with Student s t test $p<0.05$ was found in all groups except for multiparae with induced labour

DISCUSSION

As previously pointed out by Friedman (11) there is a significant difference in the clinical course of induced and spontaneous labour In our study as in that of Friedman the average duration of induced labour was about 50% shorter in both primiparae and multiparae It is evident from Fig 3 that this was mainly due to a shortening of the latent phase

Considering that the length of the latent phase is thought to depend mainly on the time needed to soften and efface the cervix (13) it is remarkable that our prostaglandin inductions in spite of significantly lower pelvic scores had latent phases of the same duration as the oxytocin inductions This is in agreement with our clinical impression that in patients induced by PGF a rapid and marked softening of the cervix was noticed during the first part of the infusion without any other signs of labour progress This phenomenon was not observed with oxytocin It gives some support to previous statements that prostaglandins are more effective induction agents in cases with an unripe cervix (2 5 26)

An obvious explanation to the short latent phase in the induction cases would be differences in the uterine activity during this part of labour Spontaneous labour often starts with weak and irregular contractions which gradually become stronger and more regular On the other hand

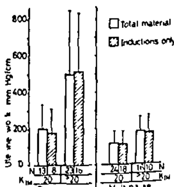


Fig 9 Uterine work (means and S D) needed per cervical dilatation during the active phase of labour patients with high and low values for K_I

essful inductions the doses of the oxytocic nt are adjusted to provoke regular and effective tractions more rapidly This would tend to relatively short latent phases in spite of the that the cervical resistance probably is greater iany cases of induction

nce labour was established remarkably small rences were found between the groups N O P and between primiparae and multiparae arding the labour characteristics frequency nsity or uterine activity Thus induced labour ld not be distinguished from spontaneous in this ject

uring both latent and active phase of labour the ine activity stayed with few exceptions between and 240 MU which is in good agreement with ious studies of the uterine activity during active ntaneous labour (6 8) This tendency explains observed negative relationship between inten and frequency during labour This has been rved previously with regard to changes in fre ncy and intensity in the same individual (7 20)

indgren (17) found in a series of spontaneous urs that for different levels of uterine activity ressed in MU it is possible to define an ideal uency which gives the highest rate of cervical tation Such an ideal frequency could not be onstrated in our series One reason for this repancy might be that Lindgren calculated the n cervical dilatation during the whole first e while we studied the latent and the active ses separately It is also possible that the oxy c drugs given to most of our patients might ve influenced the relationship between frequency intensity (23) The values shown in Fig 3 ever do not support this hypothesis Further e the fetal weight and the circumference of the l head varied probably more in our series than ie study referred to above

he amount of uterine work needed during the ve phase of labour for each cm of cervical ation showed marked differences between iparae and multiparae Remarkably low figures this variable were found in multiparae induced prostaglandins As intensities frequencies and ine activities were very similar in all groups finding confirms the generally accepted view the average cervical resistance is much less in tiparae The importance of the cervical re ince for the progress of labour is further stressed by the fact that when effective labour had been established no significant correlation could be demonstrated between frequency intensity or the total uterine activity and rate of labour progress in any of the groups

Once the uterine activity had reached the values referred to above irregular intervals between con tractions were found to have a marked negative effect on the rate of cervical dilatation during the active phase High interval variability indices (λ_I) were associated with significantly lower rates of cervical dilatation longer duration of the whole first stage of labour and a higher amount of uterine work needed per cm of cervical dilatation both in spontaneous and induced labours Variations in intensity did not seem to have this clinical signi ficance It must be stressed that no significant or even suggestive differences were observed in the interval or intensity variability between patients with spontaneous labour and labour induced by oxytocin or PGF

Diverging statements about changes in regularity of the uterine activity during labour have been put forward Krapohl (15) in a small series of multiparae found a tendency towards greater regularity with increasing cervical dilatation This was denied in another paper (9) from the same group In our study of induced patients a clear tendency towards greater regularity during labour was found only in a few cases

The results of the present investigation indicate that labour induced by oxytocin or $PGF_{2\alpha}$ in moderate doses cannot be distinguished from spon taneous labour It must however be pointed out that all patients in this series were moni tored by continuous tocographic recordings and that the rate of administration of the drugs was carefully adjusted to the degree of response in terms of uterine activity As signs of overstimula tion could rapidly be detected and the dose reduced or other types of treatment instituted the results here presented are not necessarily valid for other dose schedules or in circumstances where the drugs are administered without tocographic control

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BASIC LEVELS OF THE IMMUNO SUPPRESSIVE SERUM PROTEIN PZ IN WOMEN—INFLUENCE OF AGE PARITY GONADOTROPHINS AND ESTROGENS

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act The basic levels of the pregnancy zone protein were measured by a radio-immunoassay in 270 wom various age All women were apparently healthy g no drugs Values were correlated to age parity lotrophins and estrogens A significant age depend icrease was found for PZ while no influence could tributed to the other factors studied The present 's emphasize that the age dependent variation of PZ ntration should be considered when clinical data of rotein are evaluated

pregnancy zone protein (PZ) is a human serum ycoprotein (1 13 15 17 20) with immunosup ive properties in vitro (5 14 19) The serum entration of PZ is known to increase during nancy and estrogen treatment with individual s around 500–1 000 μg/ml (3 6 7 16 22) iously the assay of PZ has been based on elec oresis or immunodiffusion techniques with a tion limit of 10–40 μg/ml (3 16 22) A recently loped radio immunoassay for PZ with a sensi of 32 3 ng/ml has made it possible to study ow basic levels in non pregnant healthy individ and values around 8 μg/ml have been record)

e biological significance of this immuno sup- ive serum factor is not clear During preg y there is a depression of the maternal cell ated immune response (10 12) Physiological entrations of PZ inhibit the reactivity of human nphocytes (5 14) a mechanism of possible im ince for the immunological adjustment to preg y Apart from pregnancy and estrogen treat moderately increased levels of PZ (50–200 μg/ml) have been reported in patients with malig nant tumors and other diseases (2 4 18 21) How ever these reports should be evaluated with cau tion and the serum concentration of PZ in patho- logical conditions should be compared to the con centration in healthy individuals of corresponding age At present no such studies have been reported The individual variation in the PZ concentration during pregnancy and hormonal treatment is very marked and conclusions concerning the biological significance of PZ in various diseases entirely de

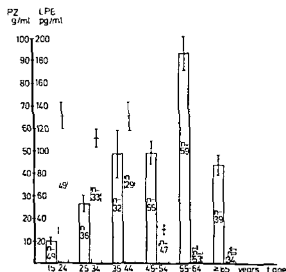


Fig 1 Distribution of mean values ±S E M for PZ μg/ml (—) and low polar estrogens LPE pg/ml ( ) in the total series according to age groups Number of investigated individuals is indicated

Table I *Correlation within age groups between the serum concentration of PZ and LPE in 245 women*

Age group	*n*	Mean±S D PZ (μg/ml)	Mean±S D LPE (pg/ml)	Correlation coefficient (ρ)	y=bx+a	(b)
15–24	49	9 9±10 6	131 3±78 6	+0 33	a=4 2 b=0 0	n s.
25–34	33	23 2±22 9	111 7±43 2	−0 20	a=34 9 b=0 1	n.s
35–44	29	48 7±57 8	130 0±69 1	−0 26	a=77 6 b=−0 2	n s
45–54	47	48 8±71 8	29 9±28 9	+0 04	a=49.3 b=0 1	n s.
55–64	53	93 1±57 1	13 7±10 7	+0 13	a=83 8 b=0 7	n s.
≥65	34	43 4±26 3	13 3± 7 5	−0 12	a=50 9 b=−0 4	n s.

pend on further knowledge of the basic levels in healthy individuals Furthermore the possible variation with age endogeneous estrogen concentration and previous pregnancies should be considered

The present communication describes the serum levels of PZ measured by radio-immunoassay in healthy non pregnant women of different age and parity The PZ concentration has been related to age parity and serum levels of LH FSH and estrogens

MATERIALS AND METHODS

blood samples were drawn from a total of 270 women of various age After coagulation all sera were decanted and stored at −20°C until use The samples were coded and tested blindly in duplicate Samples were drawn from women attending different clinics at the University hospital Umeå or Sabbatsberg hospital Stockholm for health certificates for employment or gy[illegible]ical health control All women were apparently taking no drugs Data concerning age and pari[illegible] corded Information of parity was available [illegible] only

The serum concentration of PZ (μg/ml) wa[illegible] by a recently developed radio-immunoassay (8)[illegible] ues for PZ are expressed as ng of the h[illegible] tein (13 15) per ml

In postmenopausal women age ≥55 years [illegible] tion of serum levels of FSH (n=84) and LH (n[illegible] carried out by radio-immunoassays using the Do[illegible] body Solid Phase (DASP* Organon Oss Holla[illegible] ration procedure Antibodies against FSH and L[illegible] as highly purified FSH and LH for iodination [illegible] tained from Kabi AB Stockholm Sweden [illegible] were expressed as mIU of Human Pituitary [illegible] and Human Pituitary LH or ICSH 68/40 per ml [illegible] tively

Low polar estrogens (estrone+estradiol [illegible]

Table II *Correlation within age groups between the serum concentration of PZ and parity in 113 women*

Age group	*n*	Mean±S D PZ (μg/ml)	Range parity	Correlation coefficient (ρ)	y=bx+a	Signif. of the (b)
25–34	26	21 7±18 0	0 1 2 7	+0 04	a=21 b=0 6	n s.
35–44	24	35 6±21 7	0 1 2 7	+0 09	a=32 b=1 8	n s
45–54	28	54 6±76 6	0 1 2 7	−0 29	a=82 7 b=−11 9	n s
55–64	35	97 1±58 4	0 1 2 7	−0 24	a=118 4 b=−9 8	n s

II *Correlation within parity groups between the serum concentration of PZ and age (15–60 years) hy women*

n	Mean±S D PZ (μg/ml)	Mean±S D Age	Correlation coefficient (ϱ)	$y=bx+a$	Significance of the slope (b)
70	25 3±49 6	27 8±12 2	+0 64	$a=-47\ 0$ $b=2\ 6$	$P<0\ 001$
19	42 3±35 3	39 3±12 3	+0 59	$a=-24\ 2$ $b=1\ 7$	$P<0\ 01$
33	47 8±47 6	46 0±10 4	+0 45	$a=-46\ 4$ $b=2\ 0$	$P<0\ 01$
22	66 8±66 0	51 1± 7 4	+0 43	$a=-128\ 4$ $b=3\ 8$	$P<0\ 05$

no-reactive estrogens") in serum were determined of the women by the radio-immunoassay technique vist & Johansson (9) The antibody used reacts to with estradiol 17β and to 50% with estrone (11) e values were expressed as *pg immuno-reactive* ol equivalents per ml

relation between different variables in statistical was calculated as product moment correlation (ϱ) sts of significance for co-variation were performed slope of the calculated straight line ($y=bx+a$) age groups values for PZ were compatible with umption of a normal distribution

RESULTS

nean values for serum levels of PZ and low estrogens (LPE) in different age groups of the series are shown in Table I and Fig 1 The 's indicate an age dependent increase in the PZ with the lowest mean value (9 9±1 5 μg/ml) ded for young women (15–24 years) and the t mean value (93 1±7 4 μg/ml) for women years of age ($p<0\ 001$) Thereafter a decrease PZ levels could be observed ($p<0\ 001$) With age groups no correlation was found between vels of PZ and endogenous estrogens (Ta

In order to study the influence of parity on the increase of PZ with age the correlation between PZ concentration and parity was calculated for different age groups Women in the age groups 15–24 and ≥65 years were not included for statistical reasons Within the age groups no significant correlation between PZ level and parity could be found (Table II)

Fig 1 indicates a decrease in the serum concentration of PZ in elderly women Therefore when the correlation between PZ level and age was calculated women over 60 years of age were excluded The patients were grouped according to parity (0 1 2 3) The correlation within the parity groups between the serum concentration of PZ and age is shown in Table III A significant increase till the age of 60 was found

The influence of age on the serum level of PZ is further illustrated in Fig 2 which shows the mean values ±2 S D for women between 17 and 77 years of age The PZ value for each year is calculated as the mean from observations taken from women in an age group covering the given age ±3 years

The serum levels of LH and FSH were determined in the postmenopausal women (>55 years)

IV *Correlation between the serum concentration of PZ and FSH in healthy women ≥55 years of*

n	Mean±S D PZ (μg/ml)	Mean±S D FSH (mIU/ml)	Correlation coefficient (ϱ)	$y=bx+a$	Significance of the slope (b)
53	96 6±58 0	6? ?±?7 33	−0 1	$a=113\ 0$ $b=-0\ 3$	n s
31	45 4±?7 5	51 4±?8 44	+0 04	$a=43\ 3$ $b=0\ 0$	n.s

Table V *Correlation between the serum concentration of PZ and LH in healthy women ≥55*

Age group	*n*	Mean±S D PZ (μg/ml)	Mean±S D LH (mIU/ml)	Correlation coefficient (ρ)	$y=bx+a$	Significance of the slope (*b*)
55–64	51	97 7±58 8	69 9±20 3	0 14	$a=70$ 1 $b=0$ 4	n s
≥65	30	44 [illegible]±27 2	55 2±[illegible]0 2	−0 05	$a=48$ 3 $b=-0$ 1	n s

No significant correlation between levels of PZ and the gonadotrophins could be found (Tables IV and V)

DISCUSSION

The concentration of the immuno-suppressive serum factor PZ showed pronounced variations with age Levels were rising from the age of 15 up to around 60 years This increase was independent of parity and endogenous estrogen concentration In elderly women approximately after the age of 60 years there was a decrease in the PZ concentration A tenfold increase with age in the basic levels of PZ was found when young women were compared with older ones

As in previous investigations (6 16) the variation between individuals was considerable (Fig 2) Thus PZ concentrations of 200 μg/ml were found within 2 S D from the mean value between 50–65 years of age Values of this magnitude have previously been attributed to various pathological condi (2 4 18 21) The present results emphasize that the age dependent variation in PZ con tion should be considered when such data are ated

Estrogen is believed to be important duction of PZ and the increase of this serum during pregnancy and hormonal treatment established After delivery the high serum PZ in pregnancy are reduced to non pregnant within six weeks (16) Furthermore a increase in PZ concentration is found after month of estrogen treatment (6) A pos tion between serum levels of and PZ could therefore be expected such correlation was found in any of gated age groups (Table I) The role of estr the direct trigger in the induction of P therefore be modified Estrogens must s garded as inducing factors for the synthes but there might exist some kind of phy threshold level for the action of estroge respect Also an interaction between estr other hormones must be considered T

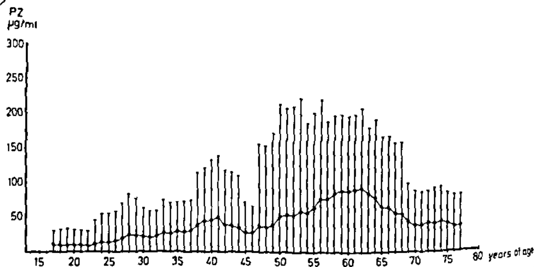


Fig 2 The mean concentration ±2 S D of PZ μg/ml at various age in healthy women between 17 and 77 years The PZ value for each year is calculated as the mean from observations taken from women in age groups the given age ±3 years

evels of estrogens and the increasing levels of
women around 50 years of age indicate the
nce of other inducing agents for the synthesis
An influence of gonadotrophins in this re
seems unlikely as there was no correlation
en levels of FSH/LH and PZ in postmeno-
l women (Tables 4 and 5) The nature of the
factors responsible for the induction of PZ
esis is at present unknown
e immuno-suppressive properties of this serum
should have biological relevance in the phy
ical adaption to the fetal allograft during preg
The mechanisms for its induction and regu
are still unknown

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DAKTAR resorberas i mycket ringa grad vid lokal applikation.
DAKTAR har goda kosmetiska egenskaper och innehåller ej lanolin eller parabener. Ett fall av sensibilisering har rapporterats. Krämen färgar ej kläderna och kan avtvättas med tvål och vatten.
Klinik DAKTAR är effektivt vid vaginiter orsakade av Candida spp. och andra svamparter. Såväl mykologisk som klinisk utläkning har konstaterats i ca 90 % av de behandlade fallen. Vid behandling med DAKTAR erhålles en snabbt insättande effekt med snabb lindring av symtom som sveda, klåda och fluor. Behandling med DAKTAR sänker förhöjda vaginala pH-värden, vilket har en gynnsam effekt på den naturliga bakterieflorans tillväxt. DAKTAR lämpar sig väl för behandling av symtomlös vaginit hos gravida och som profylax mot oral mykos hos det nyfödda barnet.
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Biverkningar I sällsynta fall (mindre än 1 %) har lätt lokal irritation rapporterats.
Dosering En fylld applikator (= 5 g kräm = 100 mg miconazol) töms djupt i slidan vid sänggåendet. Behandlingen upprepas dagligen i 14 dagar. Det är viktigt för ett gott behandlingsresultat att patienten genomför hela behandlingen. Inget uppehåll behöver göras under menstruation. Vid graviditet bör applikatorn tömmas långsamt och mindre djupt i slidan. Applikator och bruksanvisning medföljer varje förpackning.
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OCCURRENCE OF GENITAL HERPES SIMPLEX AND CYTOMEGALOVIRUS INFECTIONS IN PREGNANCY

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Eero Saksela and Pauli Leinikki

From the I–II Departments of Gynecology and Obstetrics Helsinki University Central Hospital (Heads Prof Sakari Timonen and prof Olof Widholm) and the Department of Virology Bacteriological Laboratory of Aurora Municipal Hospital (Head Prof Odd Wager) Helsinki Finland

ıct A total of 244 pregnant women 172 in the first
e in the third trimester were screened for genital
simplex (HSV) and cytomegalovirus (CMV) infec
using virus isolation cytological examination and
gical studies In addition immuno fluorescence
ig of exfoliated cervical cells was used for the de
ı of HSV infections Herpes simplex virus (HSV)
not be isolated and no characteristic HSV altered
were found in cytological (PAPA) smears Cyto
ovirus was isolated four times but PAPA smears
ed from these patients were also normal In 34
patients HSV antiserum detected immunofluo
ıce positive exfoliated cervical cells Overall 14%
ients had HSV ? antibodies and 71% CMV anti
No differences between the first or third trimes
these respects were noted

es simplex cervicitis during labour is a serious
o the newborn infant (16) Because the risk can
minished by caesarean section (1) accurate
apid diagnosis of this clinically often inappar
ıfection is important In contrast to herpes sim
virus (HSV) infection cytomegalovirus (CMV)
citis during delivery does not seem to be dan
ıs to the newborn child (14) although intra
ıe infection may cause serious damage to the
(3)

e available methods suitable for routine diag
of herpetic infections are virus isolation sero
al studies observation of cytological altera
in cervical smear preparations (PAPA) and
ıno fluorescent staining of exfoliated cervical
for detection of viral antigens

ıhmias et al (11) were not able to find herpes
lex virus infections among 175 asymptomatic pregnant women Jeansson and Molin (4) reported an 0 5% incidence of HSV infection among asymptomatic females Roughly 10% of asymptomatic pregnant women have been found to exfoliate HSV antigen containing cervical cells detectable by fluorescent antibody (FA) technique (16 25) Variable incidences up to 28% during the third trimester (14) have been reported for clinically inapparent cytomegalovirus infections among pregnant women

Cytological diagnosis of gynecological herpes simplex infections has shown approximately 70% accuracy as compared with virus isolation (13) On the other hand in a prospective study in a venereology clinic (10) cytology has proved to be even more accurate than virus isolation in preclinical cases of infection whereas in advanced clinical stages of infection with necrotizing lesions cytology may be less reliable In contrast to herpes simplex virus infections only few prospective studies exist about the value of cytology in the diagnosis of CMV infections (10 2)

Immuno-fluorescent staining for the detection of HSV antigen has been used successfully for the diagnosis of herpes simplex infections in cases where ulcerative lesions are present (7) but reports do not exist of the value of the fluorescent antibody technique as a screening method

A prospective screening study was undertaken to determine the occurrence of herpes simplex and cytomegalovirus infections in a group of pregnant women and to compare cytological virological and immuno-fluorescent methods in the diagnosis of these infections

Table I *Virological and cytological findings among 244 pregnant women*

	Study group					
	1st trimester		3rd trimester		Total group	
	n	%	*n*	%	*n*	%
HSV excretors	0		0		0	
FA positives[b]	24	14	10	14	34	14
HSV 2 antibodies	24	14	11	14	35	14
No HSV antibodies	35	20	19	26	54	22
CMV excretors	3	2	1	1	4	2
CMV antibodies	123	72	50	69	173	71
Cells suggestive of HSV or CMV infection in PAPA smears	0		0		0	
Total	172		7?		?44	

[a] 157 and 63 patients studied in the groups respectively
[b] Immuno-fluorescent staining (FA) with HSV 2 rabbit hyperimmune sera and anti rabbit conjugate

MATERIALS AND METHODS

Patients The group consisted of 244 randomly selected pregnant women attending the outpatient clinics for legal abortion and maternity care of the I-II Depart ments of Gynecology and Obstetrics Helsinki University Central Hospital A total of 172 patients were in their first and 72 in their third trimester and all were less than ?6 years old

Cytology The cytological smears obtained from the posterior vaginal fornix the ecto- and endocervix were spread across the same slide (?4) The slides were fixed with propanol fixative and stained according to Papanicolaou s original method

Immuno-fluorescent (FA) studies Cells for immunofluorescence were obtained with cotton swabs from the -- and endocervix and dispersed on slides After air -ying the slides were fixed with acetone at +4 C for four -in Immuno-fluorescent staining of fixed cells has been described earlier (7) Rabbit hyperimmune sera were used for HSV 1 and HSV 2 The sera were produced by infect ing rabbits via the ocular route The working dilutions were selected by titrating their antibody titer on infected continuous monkey kidney (BSC_1) cells Four units of type 2 antiserum and 1-1 5 units of type 1 antiserum were used In this dilution type 1 antibodies did not react with cells infected with type 2 HSV

Commercially available FITC conjugated anti rabbit gamma globulin was used as described earlier (7) Five spots were stained on each slide two with type 2 anti serum two with type 1 antiserum and one with conjugate only

Virus culture isolations Primary human embryonic fibroblasts (HES) were inoculated with samples taken with cotton swab from the cervical canal and the posterior fornix separately The samples were immediately trans ported to the virological laboratory where the inoculation took place The methods for identification of isolated viruses have been described earlier (6 8)

Serological tests The methods for anti HSV and CMV antibody assays have been described earlier (5 8)

RESULTS

Virus isolation

All patients were clinically asymptomatic 244 patients 220 could be successfully virus isolation In the remaining 24 virus cultures were destroyed by microbial growth The rate of successful i lations is presented in Table I Herpes simp (HSV) could not be isolated in any of the while four patients excreted demonstra megalovirus (CMV) Three of the latter or from first trimester patients and one from trimester patient Immuno fluorescent cytological smear preparations HSV antigen was positive in 24 first trime ten third trimester patients (Table I)

Serology

Serological studies showed that approxim same proportion of patients in early and la nancy had HSV antibodies and the same when antibody patterns compatible with activity were compared Neither did the g mean HSV titers in the two groups diffe cantly Of patients who exfoliated HSV positive cervical cells 11 were antibody and four had type 2 antibodies which corre with the general distribution in the whole s

Cytomegalovirus antibodies were demo in 173 patients (71%) Among those excret one had a moderate or high titer (over 80) a low titer (20 40) and one was sero- Neither could significant differences be

n the first and third trimester groups in the oc nce of cytomegalovirus antibodies The sero- al data are presented in Table 1

ogy

norphological signs of viral infection were seen PAPA smears included in this study Patients whom CMV was isolated were invited to a visit and another smear was taken 2–3 weeks the original samples These were also normal ough special attention was paid to obtaining ndant endocervical samples

DISCUSSION

diagnostic difficulties usually arise in patients ulcerative genital lesions but the problem lies e high proportion of asymptomatic HSV 2 in ons in pregnant women (12 22) In the present y no herpes simplex viruses could be isolated did any cytological preparation show evidence rpesvirus infections Pannu & Sigel (15) were ible to recover viruses from 229 cervico vaginal imens and HSV isolations performed by Mont ery et al (9) in 176 pregnant women with no cal evidence of HSV infection were also nega

In the present study virological samples were cted both from the endocervix and the fornix btain reliable samples for culture It has been vn that the characteristic cellular alterations ide a high degree of accuracy in the diagnosis erpetic infections (22 23) and that cytology be even more reliable in the diagnosis of pre cal cases of HSV infections than virus isola (10) Since also PAPA smears were negative results indicate the infrequency of HSV in nptomatic obstetrical patients In a recent study he present authors (22) of gynecological patients ur clinics an 0 16% overall frequency of genital / infection was detected among 57 117 PAPA ars

MV was isolated four times and all of them from ically asymptomatic patients PAPA smears all normal and even in repeated PAPA smears signs of cellular alterations compatible with V infection could be seen Although a high per age of obstetrical patients up to 28% in some s are reported to excrete cytomegalovirus typical altered cells have been reported only e in cervical PAPA smears (2 10) The reasons he difficulty in detecting CMV altered cells are not clear since under *in vitro* conditions CMV read ily infects and causes typical morphological altera tions in endocervical epithelial cells (21)

Immuno-fluorescent staining of exfoliated cells for the presence of HSV antigen has been success fully used for the laboratory diagnosis of herpetic infection in veneral and other groups of patients (7 20) Royston and Aurelian (19) were able also to demonstrate positive staining of exfoliated cervical cells from patients with cervical carcinoma In the present study however it is evident that when used for screening of asymptomatic patients the correla tion between positive fluorescent antibody (FA) staining and virus isolation is clearly inferior to the correlation found in clinically manifest cases FA positive patients in this study showed a distribution of HSV antibodies similar to the whole group 32% of FA positives and 22% of the whole series were HSV seronegative Royston and Aurelian (19) suggested that the physico-chemical conditions in exfoliated cells may give rise to an abortive viral cycle and formation of HSV specific proteins We cannot either rule out the possibility that the posi tive FA staining is not related to HSV infection but rather reflects a cross reacting antigenic structure on the surface of exfoliated cervical cells

The analysis of antibody patterns in our material revealed that the proportion of HSV 2 carriers was about the same as those obtained in other areas with socio-economically comparable populations (18) The frequency 14% is slightly lower than that in another study on the Finnish population (17) The frequency of CMV antibodies among pregnant women seems to vary according to e g socio-eco- nomic ethnic and geographic factors (14 9) In the present study 71% of the women had CMV anti bodies

In our study all the children born to mothers with positive FA for HSV or excreting CMV during pregnancy were followed through their neonatal pe riod None of them showed signs of intrauterine or neonatal HSV or CMV infection The risk to the child caused by a clinically manifest herpes simplex infection during pregnancy has been evaluated to be about 50–60% and can be reduced by abdominal delivery (1) The number of HSV 2 seropositive mothers far exceeds the number of neonatal infec tion cases indicating that only a small proportion of the asymptomatic HSV 2 carriers do transmit the virus to the baby

Although 14% of patients in the present study

had HSV 2 antibodies and 71% CMV antibodies indicating a latent infection no morphological or virological evidence could be obtained of productive infection by herpes simplex virus and only four times could CMV be isolated In the study by Nahmias et al (12) concerning cytologically detected genital herpes simplex infections during pregnancy in a low socio-economic group one per cent incidence was reported This was about three times that found outside pregnancy and puerperium in the same population Statistical analysis of the present results reveals that within 95% confidence limits the frequency of HSV infections in this population remains under 1 5% However the quite low proportion of HSV 2 antibody positive patients in this group as well as the earlier retrospectively detected 0 16% frequency in our general outpatient population (22) would point to a lower incidence than that reported by Nahmias et al (12)

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SIMPLE HYSTERECTOMY IN THE PRESENCE OF INVASIVE CERVICAL CANCER

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act During the years 1956–69 74 cases of invasive al carcinoma treated by simple hysterectomy were d to the Norwegian Radium Hospital The 5 year al for those with free operative borders was 77 1% mpared with 30 7% for those cases in which the r was transected during operation Before operation upposed benign condition cancer should always be out If simple hysterectomy is performed and cervi ncer found in the specimen immediate postopera egavoltage radiotherapy affords the best chance of

accepted methods of treatment of invasive al cancer are either radical surgery radio- py or a combination of both All workers in eld agree that simple hysterectomy is an in iate form of treatment Various authors have ted series treated inadequately in the first in and offered suggestions for improvement in diagnostic accuracy and salvage In 1968 r Pece & Brunschwig suggested that early t surgery offered the most comprehensive py in the shortest time In their opinion delay form of preoperative radiotherapy severely promised the chances of cure On the other Cosbie proposed radiotherapy as a reason lternative to radical surgery for salvage Both s however offered poor prognoses 1973 Andras Fletcher & Rutledge presented a of 148 cases in which they reported that in rly stages of the disease the prognosis may be od as in those treated more conventionally ded radiotherapy was given immediately after rectomy The most obvious way to reduce the er of patients inadequately treated is to im the standard of preoperative assessment in all its being operated for supposed benign conditions with special emphasis on the exclusion of cancer Ideally this assessment must include adequate visualization of the vulva vagina and cervix cytological examination of the cervix the smear being taken from both the endocervical canal and the posterior fornix colposcopic examination and biopsy of any suspicious lesions and fractionated curettage if the transformation zone cannot be clearly seen or the patient has suspicious symptoms Only after these investigations have been made can one be reasonably satisfied that the patient is ready for surgery

This report deals with experience at the Norwegian Radium Hospital in managing the patient treated by simple hysterectomy for a presumed benign condition only to find carcinoma of the cervix in the operative specimen at histological examination

CLINICAL MATERIAL AND MODE OF THERAPY

In the years 1956–69 74 patients were referred for further treatment to the Norwegian Radium Hospital after their initial operation had proved inadequate Of these 48 have been observed for at least 10 years During the same period 4492 patients with invasive cervical cancer received all their treatment in the hospital

Table I lists the preoperative diagnoses As many as 28 of these women presented with a cancer suspicious history of metrorrhagia Another 3 were operated with a simple hysterectomy after a positive diagnosis of cancer had already been made at biopsy Thus there are 31 in the series who had incompetent medical care Many of those with a history of menorrhagia had been curetted several times before with negative findings Two were operated upon for pelvic sepsis one with bleeding in pregnancy and one who presented with a subacute intestinal obstruction

Only cases with proven histological evidence of invasion have been considered all cases of microinvasion

Table I *Indications for hysterectomy*

Intermenstrual and/or post-coital bleeding	16	31
Post menopausal bleeding	3	
Bloody discharge	9	
Invasive cancer	3	
Carcinoma in situ		4
Myoma uteri		3
Menorrhagia		11
Others or unrecorded		25
Total		74

(stage I a) are excluded For ease of comparison we have divided the cases into groups (Table II) such that group I corresponds to clinical stage I b group II represents those with known gross disease cut through at operation and referred within 6 months of the original surgery whilst group III are those with tumour transected at operation but whose follow up treatment was delayed more than 6 months In this scheme we have followed roughly the guide set by Andras et al (1)

There were 65 (87 8%) squamous cell carcinomas and the remaining 9 (12 2%) were adenocarcinomas adenosquamous or undifferentiated carcinomas

60 (81%) were less than 60 years old whilst the average age was 48 9 (Table III)

Most patients were treated with intravaginal radium and external radiotherapy Initially this external therapy was delivered by orthovoltage machines but after 1958 either a 31 MeV Betatron or a 60C machine was used Table IV shows the methods of irradiation Two patients had supravaginal hysterectomies and these received radium into the cervical stump in addition to intravaginal radium external megavoltage therapy During the early years this study there was no set system of treating these tients and this is reflected in the spread of therapeutic regimes The majority received radium and megavoltage therapy In recent years standard treatment has been external megavoltage radiation delivering 5 000 rad in the

Table II *Findings at operation and time of referral*

Patient group		Observation time	
		5 years	10 years
I	Free operative borders (stage I)	48	29
II	Not free borders referred within 6 months	16	12
III	Not free borders referred after 6 months	10	7
Total		74	48

Table III *Age distribution*

Age	Numbers
40–49	11
50–59	31
60–69	18
70–79	11
80–	3
Total	74

midpelvic plane In the earlier years of the study orthovoltage machines were used the dose was about 3 000–4 000 rads

RESULTS

Tables V and VI show the status of the pa... and 10 years Of the 74 in the study 45 we... and free of disease at 5 years giving survival of 60 8%

Considering group I the 5 year ... 77 1% In this group there were 2 patients died of incurrent disease—one of a haemorrhage and the other of lymphat... kaemia Autopsy revealed no evidence o... disease A further 3 were alive after 5 years with active disease None was considered s... for surgery one received Thiotepa and Ge... therapy for an adenocarcinoma recurrence ... the 3 she is the only one living now 9 months beginning this treatment

In group II the 5 year survival was 37 ... patient had a transurethral resection for a recurrence after 2 years and is now alive ... evidence of disease 12 years after therapy

As could be expected the results in gr... were not nearly so good—20% at 5 years w... one was alive after 10 years

Table VII records sites of recurrence of d...

Table IV *Method of irradiation*

	Patient group		
	I	II	I[illegible]
Vaginal radium	7	1	[illegible]
Radium + orthovoltage	6	[illegible]	[illegible]
Orthovoltage	–	–	[illegible]
Radium + megavoltage	24	8	[illegible]
Megavoltage	11	4	[illegible]
Others	–	1	[illegible]
Total	48	16	[illegible]

V *Status at 5 years*

t	Alive	Alive with disease	Dead of cancer	Dead of intercurrent disease	Lost to follow up
	37 (77 1%)	3	4	2	2
	6 (37 5%)	–	10	–	–
	2 (20 0%)	–	8	–	–
	45 (60 8%)	3	22	2	2

dless of time interval after treatment Pelvic rrence was by far the most common either or in combination with distant spread seen ially in the more advanced cases In this there were 13 whose cause of death was ded as uraemia as a result of ureteric obstruc n the pelvis

nsidering that these patients were mishandled ially the complications were surprisingly few two major ones were both found in group II first had a local resection of a bladder recur – which eventually resulted in a chronically racted bladder requiring urinary diversion is alive and well with an ileal bladder 12 years r initial therapy The other had severe radiation ige to the bowel with multiple fistula forma I She had several operations including col ny and ureterostomy but died 2 years after py from chronic renal infection and electrolyte rbance She had received radium and 3000 megavoltage

Table VII we see the fate of those with adeno- noma From this small series one cannot see difference in behaviour from those with mous carcinoma but the overall figures are too I All those still living have survived for at least ars since the time of diagnosis Recurrences followed the common trend predominating in elvis

VI *Status at 10 years*

it	Alive	Dead of cancer	Dead of intercurrent disease
	23 (79 0%)	4	2
	4 (33 3%)	8	–
	0 0	7	–
	27 (56 2%)	19	2

COMMENTS

Group I of the present series showed a relatively high 5 year survival rate As a matter of fact com parison with the survival figures for stage I b lesions treated conventionally at the hospital during the same time period did not reveal any difference This reflects surely the selection of operative cases Only those who are relatively young and fit are candidates for surgery for benign conditions Furthermore the tumour was in most cases very small It should be emphasized however that all of them showed invasion more than 5 mm into the stroma

As expected the prognosis was poor in those cases where the tumour was transected during operation The poorest prognosis concerned group III where follow up treatment was delayed more than 6 months after simple hysterectomy The re sults presented here are in complete agreement with the series published by Andras et al (1)

From our series of only 9 cases of adenocarcinoma we cannot draw any firm conclusions but it would appear that the prognosis in adenocarcinoma is no worse than in the squamous disease

Table VII *Sites of recurrence*

Sites of recurrence	Patient groups I	II	III	Total
Vagina and pelvis	1	–	1	2
Pelvis	4	4	2	10
Vagina and distant metastases	1	–	–	1
Pelvis and distant metastases	–	3	3	6
Distant metastases	1	2	2	5
No of recurrences/ Total No	7/ 48	9/ 16	8/ 10	24/ 74

The obvious conclusion of the present study is that it is still necessary to improve the standard of preoperative assessment in all women being operated for supposed benign conditions All cases should be fully screened preoperatively using cytology colposcopy biopsy of any suspicious lesion and if indicated fractionated curettage If in spite of these measures an occasional case of invasive cancer is overlooked immediate postoperative megavoltage radiotherapy should be given so as to ensure the best chance of cure

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ULTRASONIC DIAGNOSIS OF PLACENTA PRAEVIA

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act 741 women suspected of placenta praevia were itted to ultrasonic scanning during the second and/or trimesters of pregnancy In 61 an abnormal placental as diagnosed During Caesarean section carried out of these cases the location was compared with the ound findings The scanning diagnosis during the imester correlated with the findings at delivery At ing after the 35th week the diagnosis differed in only es In all 4 there was a question of a low lying nta versus partial placenta praevia During the sec rimester diagnoses of low lying placenta were re in several cases at later scans It is discussed ier these early diagnoses of an abnormal placental which later becomes normal indicate a migrating nta and/or an uncertainty of the scanning method diagnosis of low lying placentae should be checked peat scans

rmination of placental location has always of importance in obstetrics especially in pa s with bleeding episodes during pregnancy or resentations Recently increased use of diag ic amniocentesis has created a need for ac te location of the placenta at all stages of preg y

nce 1966 (5 6) ultrasound scanning has gained asing ground in placental diagnosis especially the ultrasonic equipment had been improved 970 to visualize also placentae located on the erior wall of the uterus (15)

omparative studies have shown results equiva with other diagnostic methods such as soft ie X rays (1) and isotope scanning (2 3 4 and However ultrasound scanning is preferred cially because of its better delineation of the ental border Ultrasound scanning immediately re Caesarean section has given an almost 100% ement with the operative findings in placental tion (6 15)

At ultrasound scanning at different stages of preg nancy there is an increasing discrepancy between the diagnosis and the results at term the earlier the ultrasound scanning is performed Thus Kukard (12) found a difference of 17.3% when scanning was done before the 30th week 11% between the 30th and 34th week and 4% between the 35th and 40th week Despite the diagnostic uncertainty ultrasound scanning is still the only applicable method for locating the placenta during early preg nancy

MATERIAL AND METHOD

The material comprises 741 patients scanned by ultrasound during the second and third trimesters of preg nancy for the purpose of locating the placenta The indi cations were bleeding during pregnancy or irregular pre sentations Of these patients 182 were examined during the second and 559 during the third trimester Partial or total placenta praevia or low lying placenta (8 2%) were diagnosed in 61 patients These 61 patients had a total of 145 scans 46 during the second and 99 during the third trimester Forty six were delivered by Caesarean section

The ultrasound scans of the placenta were carried out as routine examinations by the Ultrasound Laboratory staff Determination of the placental site during the Caesarean sections was done by the changing members of the surgi cal staff

The ultrasonic equipment was Eskoline 20 rebuilt for B scanning Diasonograph NE 410? and Diasonograph NE 4102 B

RESULTS

Table I lists the ultrasound diagnoses and the find ings at delivery in 63 patients In the case of differ ent scanning results the last one is indicated by an arrow

Fourteen consistent investigations showed total



Fig 1 Longitudinal scan Symphysis at left Total placenta praevia (arrow) Ultrasonic scanning in the 37th week of gestation

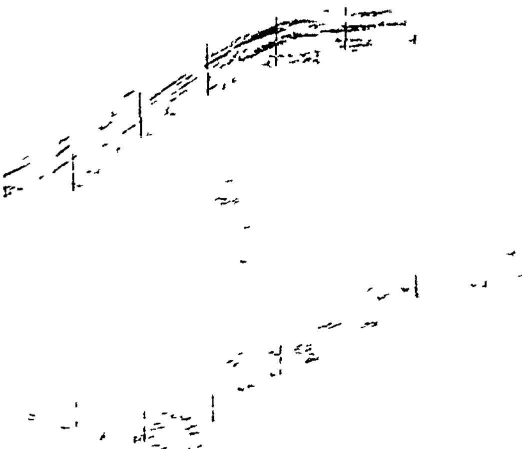
centa praevia (Fig 1) In these cases all the ultrasound diagnoses were finally confirmed during the third trimester In one case diagnosed by scanning as total placenta praevia the diagnosis at delivery was partial placenta praevia Two patients had a scanning diagnosis of total placenta praevia during the 14th and 17th week respectively Both were re scanned in the third trimester and at that time the location of the placenta was normal in both but low on the lateral walls

Five partial placentae praeviae were consistent In four cases a placenta praevia diagnosed as partial at delivery had been deemed total during scanning and in two cases diagnosed at scanning as partial placenta praevia operation showed low lying placentae In seven cases partial placenta praevia had been diagnosed during the second trimester Six of them were re scanned during the third trimester and then showed a normal location Of these seven patients four had posterior wall pla two lateral wall placentae and one an a en placenta (Figs 2 and 3)

All 26 patients in whom ultrasound scanni cated low lying placenta had been scan the third trimester Of these 16 accorded operative findings two were found to hav placenta praevia and two partial Th were posterior wall placentae Six cases d at the first scanning as low lying placentae a normal site when re scanned All six patients primarily abnormal findings had posterior or wall placentae

In two cases in which the ultrasonic dia was a normally situated placenta Caesarea tion revealed total and partial placenta re spectively One was bipartite and the ot placenta membranacea

All the remaining 658 patients had a



Longitudinal scan Symphysis at left Partial :a praevia (arrow) Ultrasonic scanning in the 24th f gestation

I *Sixty three patients in whom ultrasonic scanning or diagnosis at delivery showed abnormal ation of the placenta*

ound diagnosis				Diagnosis at labor			
lete ta a	Partial placenta praevia	Low lying placenta	Upper segment placenta	Complete placenta previa	Partial placenta previa	Low lying placenta	Upper segment placenta
				14			
					1		
			2				2
	5				5		
	4			4			
	2					2	
	7→		6				7
		16				16	
		2		2			
		2			2		
		6→	6				6
			1	1			
			1		1		

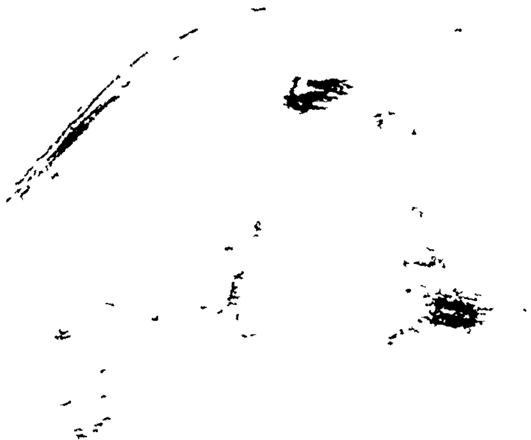


Fig 3 Longitudinal scan Symphysis at left Same patient as in Fig 2 now in the 34th week of gestation Now the placenta is normally situated on the anterior u... (arrow)

ated placentae at ultrasound scanning as well as partu

DISCUSSION

Analysis of the results suggests two factors in particular which require further assessment

In the first place the agreement between ultrasonic diagnosis and assessment at delivery seems the worse the earlier the scanning has been performed

The second problem is the difficulty involved in the exact visualisation of the lower margin of the placenta especially on the posterior and lateral walls

It is apparent firstly that placentae deemed at scanning during early pregnancy to be low lying are often found to be located the higher in the uterine cavity the closer to term the scanning is repeated This is in accordance with the findings of Hellmann (7) At ultrasound scanning du... first trimester he found only 1/10 of the... implanted ova to be clinically placenta ... at term An interpretation of such discrepan... being due to an erroneous first diagnosis ... unjust however

In general the placenta is believed to be ... given site in the uterine cavity but several ... may account for an altered placental p... Around the 16th week the placenta covers ... uterine cavity but at delivery only betwee... third and one-quarter Thus the original re... ship between the placenta and the uter... change in the course of pregnancy The incr... uterine growth is not equal in the upper and... segment While the upper segment increases... in mural thickness the lower segment grows ... through stretching and distention of the ... fibres This contributes to increasing the ...

een the lower placental margin and the inter
os

he uneven growth of the uterine layers also
es shifts in the placenta which according to the
ry of King (10) must entail changes in its posi
and immediate repairs if an abruption is not to
lt

or technical reasons an exact visualisation of
ower margin of a low lying placenta is difficult
4) especially during early pregnancy (12) This
ies particularly to placentae situated on the
erior and lateral walls as adequate filling of the
der affords a more precise diagnosis in the case
nterior wall placentae If the foetus is lying high
ne uterus there is a tendency to under estimate
distance to the os because the area is not dis
'ed by the foetus But if the head is well down in
pelvis it may cover the impulses so that a
edge of a posterior or lateral wall placenta is
properly visualised To elucidate these factors
e is a possibility of using Donald s full bladder
inique (5) or Sander s water pessary (13) By
ns of a special pessary—filled with water and
ed at the vaginal fornix—the poor visualisation
osterior and lateral wall placentae may be im
ved

he appearances around the lower margin of the
enta are more distinct close to term In ques
able cases therefore a repeat scan should be
ommended as close to term as possible

n the present analysis there were no false posi
or false negative results after the 35th week but
e were four cases of divergent interpretations
cerning the diagnosis low lying placenta partial
enta praevia or total placenta praevia (6 3%)

he two false negative results that occurred were
ipartite placenta in which only one part was
ualised and a placenta membranacea whose
gin in the lower segment was not visualised
h were scanned before the 34th week

he other differences apparent from Table I do
decisively reduce the value of the method In
evaluation regard must be paid to the fact that
Caesarean section was carried out at different
nes of labour and by changing surgeons Both
se influenced the operative assessment regarding
ental location

t must be concluded that in a number of cases
placenta migrates towards the fundus in the
rse of pregnancy and that visualising the lower
gin of posterior wall and lateral wall placentae
may give rise to technical difficulties During the last month before term the migration has been completed and the lower margin of the placenta is better visualised In all abnormal cases therefore the placental scanning should be repeated within the last month before term to decide the mode of delivery

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NEGATIVE SMEARS IN WOMEN DEVELOPING INVASIVE CERVICAL CANCER

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act Fifty six cervical smears originally classified as I from women in whom cervical cancer of stage I ′ was detected within 4 to 5 years after the cyto- al check were re-examined in order to estimate the ning error and sampling failure At the review 35 rs were classified as Pap II to V The incidence of ed classification of the smears obtained from popu ı screening was 70% and that of the smears taken at te specialists or at hospitals was about 50% The in ce of sampling failure on the evaluation of the smears fied as Pap II should be considered On 14 slides ctly interpreted as negative there were no columnar present a fact that may indicate inefficient sampling ls from the squamo-columnar junction

s been proposed that there is an average dura of about 12 years between preclinical and in ʼe cancer of the cervix (4) Some authors ob d a high frequency of negative smears pre ıg an invasive cancer within a much shorter however (4 6 11) There are various reasons this for instance false negativity due to in cient sampling of material or incorrect evalua of the cells The trauma to the cell surface of ervix due to vaginal washing or coitus has also ı considered (8) The cancer might be situated eper layers or endocervical cavities thus caus ow exfoliation of cells Certain tumours seem ıve a short preclinical stage and may arise and ress in between two cytological checks (1) The ɔgical variability in exfoliation of cells from ıe should also be borne in mind

ıe purpose of this study was to find out the ɔns why 56 smears belonging to women in m cervical cancer was detected within 4 to 5 s had been classified as negative that is Pap I smears were re-examined in order to estimate the rate of screening error and sampling failure The presence of low exfoliating and/or rapidly growing cancers is discussed

MATERIAL AND METHODS

The material consists of the women invited to the cyto- logical mass screening of the city of Stockholm in the years 1968 to 1974 in whom cervical cancer of stage I to IV was diagnosed within the same period The patients were looked for in the registry of the Department of Gynecological Radiotherapy Radiumhemmet and as a cross check also in the Registry of Cancer at the Swedish Board of Health and Welfare Details of the way of collecting the material was described elsewhere (11)

In Sweden the triple smear containing specimen from vagina ectocervix and endocervix is practised (14)

Out of 177 women included 64 had got at least one negative smear within 4 to 5 years prior to detection of the cancer and 5 of them had got 2 negative smears within the same time Thus a total of 69 smears were searched for at the laboratories Fifty six slides were obtained Six slides had been discarded at the laboratories where they were first examined The remaining 7 slides were not found in spite of an extensive search

Negative smears belonging to women in whom cervical cancer or its preclinical stage had *not* been detected 5 years later were also added The cytologists reviewing the smears were told about this fact but not of the number of these 7 control slides Neither were they informed of the stages of cervical cancer detected and dates of diagnosis in the rest of the women

Twelve of 26 smears obtained at private specialists or at hospitals and all 30 smears from the cytologic population screening in Stockholm were originally examined at the same laboratory where the review took place Two cytologists one cytopathologist and one cytotechnician re-examined the slides of the mass screening and the control smears Unexpectedly it was impossible to have the remaining slides reexamined by more than one of the screeners

Table I *The frequency of negative smears correlated to time of birth of women developing cervical cancer*

Year of birth	Number of women with cervical cancer	Frequency of negative smears	
		No	%
1914–15	32	6	19
1920–24	40	13	32
1925–29	32	10	31
1930–34	52	25	48
1935–39	21	10	48

Columnar cells were especially looked for on the slides finally interpreted as negative The presence of this type of cell may indicate an adequate collection of material from the squamo-columnar junction in case it is situated deep into the endocervical canal

RESULTS

The rate of negative smears in women of different age groups is shown in Table I Negative smears were more frequent among the younger women developing cervical cancer compared to the older ones In Table II the distribution of correctly and falsely interpreted smears is demonstrated and related to the stage of cancer detected Twenty one smears were correctly negative that is classified as Pap I and 35 were judged as atypical at rescreening Table III shows the final interpretation of ears primarily reported as negative on the one d of those women in whom cervical cancer was etected *within 4 to 5 years and on the other of* the controls that is women in whom cervical cancer had *not* been observed within 5 years The frequency of incorrect evaluation of the smears taken at mass screening is as high as 70% and that of smears taken elsewhere is about 50%

Out of 21 correctly judged smears columnar cells were present on 7 slides only In 4 cases of these dysplasia had been observed at an earlier check Five patients obtained 2 negative smears within 4 to 5 years prior to detection of the cancer In 2 of these women at least both smears were correctly negative The time interval between the smears finally judged as negative (Pap I) and the dates of diagnosis of the invasive cancer is seen in Table IV None of the women with correctly negative smears had got any symptoms at the date of the cytological check Neither were there any visible changes on the cervix Three of the women dev adenocarcinoma of the cervix

Adenocarcinoma was observed in 12 patie endocervically situated squamous cancer in 8 177 patients of the series Eleven of these had had a negative smear Only six slides w examined since the rest could not be obtained of them proved to be incorrectly negative least 12 patients with the mentioned types of had had atypical smears though in all cases normality concerned the squamous cells

DISCUSSION

Several workers noted a high percentage o negativity in cytological screening (3 17 19 authors assumed this being due to a high incorrect interpretation of the smears bu based their statement on indirect proof onl 9) Pedersen however in re-examining 17 primarily classified as Pap I or II observed falsely evaluated (10)

In the present study only smears classi Pap I are included to the group of negativ since they lead to no further action Smea sified as Pap II as well as the more ab changes give rise to follow up in one way o Accordingly the 56 smears of this study or interpreted as Pap I were divided into 2 after rescreening those correctly negati those incorrectly negative In this way the ing error is shown to be about 60% (Table ler et al of British Columbia noticed a s error close to 50% in re examining 6 originally judged as negative (4)

The false negativity in cytological che overt cancer of the cervix has been pointed Necrotic tissue may prevent exfoliation of nant cells However in the present study n

Table II *The final classification of vag al earlier reported as negative related to s cervical cancer detected*

Stage of cancer	Negative	Atypical
I A	2	4
I B	15	18
II–IV	4	13
Sum	21	35

III *The final interpretation of smears originally classified as negative*

valuations of 2 cytologists are reported of the smears taken at mass screening and of the control slides s= nous cells

	Cytological classification						
	SI SI	SII SII	SII SIII	SIII SIII	SIII SIV	SIV SIV	SIV SV
rs of women checked at mass ing in whom cervical cancer detected within 4 to 5 years	9	9	3	4	2	1	2
of women checked elsewhere cervical cancer was cted within 4 to 5 years	12	11		3			
rs of women in whom cervical er had *not* been observed 5 years (controls)	5				2		

hanges were visible at the time of cytological king performed at least 5 months prior to de on of the malignancy

ie extremely high frequency of incorrect ation of the smears taken at mass screening) may be explained by the monotonous rou hecking Considering the number of smears to reened (700 000 a year in Sweden) and the fact 98% are negative the problem is somewhat il nated The cytotechnicians might fail in their tion because of the uniformity of the slides over at certain laboratories there is a habit of ining slides from the mass screening late in the noon when the cytologists may be exhausted adding some known abnormal smears to a cer number of routine slides the watchfulness t be tested Also frequent changing of the type aterial would help to counteract the monotony duced number of routine smears per cytologist ld raise the quality of screening

n fourteen slides with normal squamous cells olumnar cells were seen a fact that might in e an inadequate sampling of material from the mo-columnar junction It could never be proved however Technical failure in specimen collection contributes to complicate the interpretation of the cells and may influence the classification of smears to Pap I or II In fact sampling inefficiency has been paid attention to as the most important reason for false negativity and there is a proposal always to take two smears at a time to diminish the risk of failure in specimen collection (13) Double sampling and checking would thus also help to raise the correctness of evaluation of the cells For practical reasons 2 smears taken simultaneously are preferable to sampling on different occasions

Adenocarcinoma or endocervical cancer may be difficult to detect by cytology due to low exfoliation of cells or to inaccessibility In this series a good half of the women developing these types of cancer had had suspicious smears In no case were there abnormal columnar cells present however

Only 6 women in this series had smears with normal squamous cells containing columnar cells as well It is hard to say whether in these women there developed a cancer with a very short preclinical stage since a biological variation of exfoliation of cells should also be considered

e IV *The time interval between smears finally ified as Pap I and the dates of detection of the er related to stage*

of r ted	Time in years			
	0 5≤1	≤2	≤3	≤4 to 5
ı	3 1	5	3 2	4 1

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ULTRASTRUCTURE OF THE HUMAN PLACENTA AT TERM

Observations on Placentas from Newborn Children of Smoking and Non smoking Mothers

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act The placenta was chosen as a possible model for sting the vascular injury and tissue injury provoked bacco smoking in the human body Full term ntas from 4 smokers and 3 non smokers were studied transmission electron microscope Pronounced es were found in the group of smokers The cteristic findings were broadening of the basement rane of the placental villus increase in collagen nt of the villus decrease in vascularisation and mu hanges in the villous capillaries and arterioles with unced intimal oedema Since similar changes have reported previously from human umbilical arteries ince these changes also can be induced in animal es by exposure to carbon monoxide or perfusion icotine this study supports the concept that tobacco ing is harmful to the human vascular system and s

icco smoking during pregnancy causes compli ns a higher incidence of abortion and small ate children (1 3 7 12 14 18)
nong the newborn children an increased mor rate is found compared with children of non king mothers Some investigations have over pointed out that smoking mothers are likely to have female offspring (2 8 12)
e have recently published an investigation on a p of heavy smokers Ultrastructural research been performed on the umbilical artery and re intimal damage had been demonstrated (2)
e placental weight as well as the weight of the lren born of smoking mothers is low compared that of non smokers (2 12) As the umbilical y showed impressive intimal damage in the tron microscope it was considered of interest valuate the damage to the placenta caused by cco smoking

MATERIAL AND METHODS

Patients

A group of 7 patients—4 smokers and 3 non-smokers—was examined All patients were examined by the same investigator and each patient completed a questionnaire on smoking habits before and during pregnancy

Non-smokers were patients who had never smoked before pregnancy and who had smoked no cigarettes at all during pregnancy Smokers were patients who have smoked a lot before pregnancy and who still smoked All smokers were inhaling cigarette smokers One subject smoked 40–60 cigarettes/day

Women suffering from hypertension diabetes mellitus or other illness and those with Rhesus negative blood type were excluded from the material The patients selected for the investigation were clinically healthy and normal before and during pregnancy

All routine laboratory tests (haemoglobin blood sugar etc) including urine analysis for blood sugar and albumin were normal

Oestriols in urine were not systematically examined throughout the pregnancy but random tests revealed normal values

The only difference between the two groups was smoking habits

Clinical data are presented in Table I All patients were white had normal pregnancies and gave birth to children at term All children were mature and no malformations were found

The mean weight of the children in the smokers group was 3 506 g in the non smokers group 3 933 g—a difference of 4?8 g

The mean weight of the placenta in the smokers group was 730 g in the non-smokers group 850 g—a difference of 1?0 g Macroscopically the placentas of smokers were more fibrotic and less loose than those from non-smokers

In the smokers group 1 boy and 3 girls were born—in the non-smoker 3 boys

Biopsy and preparation for electron microscopy

Immediately after delivery of the placenta small blocks were cut out and placed in 4.5% cold purified

Table I *Clinical data*

	Mother				Child			Placenta		
Cigs/day	Pregnancy number	Age (y)	Weight before pregnancy (kg)	Height (cm)	Birth weight (g)	Birth length (cm)	Sex	Weight (g)	±days to term	[illegible]
0	1	23	55	173	3 800	50	M	750	+14	[illegible]
0	3	36	52	164	3 900	52	M	950	[illegible]	[illegible]
0	1	24	60	170	4 100	53	M	850	+10	[illegible]
10	1	17	51	170	3 450	[illegible]	F	780	−3	[illegible]
[illegible]0	1	19	52	162	3 343	51	M	750	−6	[illegible]
30	4	30	60	176	3 990	54	F	780	−11	[illegible]
60	1	31	69	175	3 250	50	F	610	0	[illegible]

glutaraldehyde containing 2% acrolein and buffered to pH 7.4 with 0.2 M phosphate buffer for one hour. Post fixation was carried out in 1% buffered osmium tetroxide (pH 7.4) for one hour at 4 C. The tissue blocks were dehydrated in graded ethanols, cleared in propylene oxide and embedded in Epon 812 or Araldite (Durcopan ACM). Sections 0.5–1.0 μm thick were stained with toluidine blue for light microscopy. Ultrathin sections were cut on glass knives with an LKB Ultratome III, mounted on uncoated copper grids and contrasted with magnesium uranyl acetate and lead citrate. These sections were examined and photographed in a Zeiss 9S ? electron microscope.

The present study is an extension of a previous published work on the umbilical artery. The artery was the main source for research and therefore, depending on time limits for preparation, only few placentas were acceptably prepared for transmission electron microscopy.

The photographic work and the following description of he morphology was completed and the patients classified smokers or non smokers before breaking the code.

RESULTS

Non smokers

In the *non smokers* group the placental villus was covered on the surface by the syncytiotrophoblast often consisting of polynucleated cells. The luminal plasma membrane formed numerous microvilli. In the dark cytoplasm, containing highly developed rough endoplasmatic reticulum, the usual organelles were present, i.e. golgi, nucleus and nucleoli, mitochondria. Glycogen rosettes were also present. The basal plasma membrane formed numerous pedicals stretching into the villous stroma (Fig. 1).

Beneath the syncytiotrophoblast was the cytotrophoblast. These cells did not always form a continuous layer of cells, but often lay separately one by one.

The cytotrophoblast cells were pale with rough endoplasmic reticulum and ordinary c... les.

The syncytiotrophoblast and the cytotroph... were connected by many desmosomes.

In the cytotrophoblast the basal p... membrane often formed a small canal with ... connection with the nuclear envelope.

The basement membrane separated these layers of cells from the villous stroma. The ... ment membrane formed a continuous band width ranging from 50–150 mμ (Fig. 1).

The villous stroma was highly vascula... capillaries consisting of endothelium of norma... pearance with tight junctions. The endotheli... showed a fine fibrillary structure and benea... cells there was a thin non-continuous b... membrane.

The villous stroma contained a sparse substance with few collagen fibres and fibro...

Smokers

In the *smokers* group the same architectu... found in the syncytiotrophoblast. Loss of the l... nal microvilli was a characteristic finding. T... was often blebbing in the microvilli. The cytiotrophoblast layer appeared flat com... with that of the non smokers, due to loss of c... plasm, and there was protrusion of the nucle... the lumen (Fig. 2). The amount of rough e... plasmic reticulum and mitochondria corresp... to that of the controls. A slight dilation of the r... endoplasmic reticulum due to a dark homoge... mass was occasionally found.

The cytotrophoblast layer situated beneat...



1 Surface of human placental villus at term from a smoking mother *L* Lumen *S* syncytiotrophoblast *V* microvilli *ER* endoplasmic reticulum *M* mitochondrion *BM* basement membrane Bar indicates 1 μm



Fig 2 Surface of hum[an pla]cental villus at term fr[om a] smoking mother [...] day) Note the [...] the basement membra[ne] [...] decreasing [...] plasm in the [...] blast and the increase [in] collagen amount in the [...] stroma. *L* Lumen *S* syncytiotrophoblast *C* cytotrophoblast *BM* [base]ment membrane Bar [...] 1 μm

syncytiotrophoblast consisted of fewer cells but there were no essential differences compared with the nonsmokers The connection between the two cell layers was looser with loss of desmosomes

The basement membrane was considerably widened often of width equal to that of the luminal cell layers The syncytiotrophoblast formed long cytoplasmatic processes with extension into the basement membrane giving it a zig zag course The pedicals seen in the controls were not present

An important finding was the obvious decrease in vascularisation with loss of capillaries The endothelium in the vessels was characteri[zed by] oedema The luminal endothelial plasma me[mbrane] was studded with blebs (Fig 3) The n[umber of] closed junctions was decreased and th[ey] were surrounded by a continuous broaden[ed base]ment membrane often forming blocks of me[mbrane] material

Another characteristic finding was the sig[nificant] increase in collagen content in the villous st[roma]

The morphological changes are present[ed] quantitatively in Table II graded on a scale f[rom ...] to ++++



Endothelial lining in placental arteriole deriving a placenta at term form a smoking mother (60 ciga day) Note surface blebbing of the endothelium *L* Lumen *ER* erythrocytes *E* endothelial cell *B* cyto plasmic process forming a surface bleb *BM* basement membrane Bar indicates 1 μm

Table II *Ultrastructure of human placentas at term from 3 non smokers and 4 smokers*

The morphological changes were graded on a scale from + to ++++ The most marked differences were the b[illegible] the villus basement membrane the increase in amount of collagen and the poor vascularisation in the smokers [illegible] arterioles and capillaries oedema with blebbing was seen combined with loss of tight junction in the end[illegible] formation of a continuous basement membrane On the villus surface the number of microvilli seemed to de[illegible] increase in tobacco consumption

Cigs/day	Continuous basement membrane width	Stroma amount of collagen	Stroma vascular degree	Arterioles Oedema (blebbing)	Arterioles Continuous basement membrane	Arterioles Tight junctions	Cy[illegible] blast (n[illegible] cel[illegible]
0	+	+	++++	−	−	++++	++
0	+	+	++++	−	−	++++	+++
0	+	+	++++	−	(+)	++++	++
10	+	++	+++	+	+	+++	++
20	++	++++	++	+	+	++	++
30	++++	++++	+	++	+	+	+
60	++++	++++	+	++++	+	+	+

DISCUSSION

The macroscopic microscopic and ultrastructural appearance of the human placenta at term from normal pregnancies has been well described (6 11 17) The controls in this present material correspond to these descriptions The basement membrane beneath the syncytiotrophoblast and the cytotrophoblast have not been described in detail but appear from the electron micrographs (6 11 17) to be comparable with the present controls It is indicated that the average width is 150 $m\mu$ (11)

No ultrastructural research in placentas delivered by heavy smoking mothers has been published to date The present investigation on human placentas at term is an extension of a previously published work dealing with the ultrastructural changes in the umbilical artery from heavy smokers (2) That investigation (2) elicited the information that tobacco smoking causes severe intimal changes in the human vessels Similar damage has been demonstrated in animal exposure studies (4 10)

In the present study two particularly heavy smokers with a consumption of 30 and 60 cigarettes per day were examined Both patients were included in the umbilical artery study (2)

The normal structure of the human placenta at term consists of the placental villi containing the capillaries with the fetal blood The villi are covered with the later atrophying cytotrophoblast situated beneath the syncytiotrophoblast These two cell layers form the barrier towards the maternal blood flow The placental barrier consists of the different layers in the capillaries the villous strom[illegible] basement membrane and the two cell layers [illegible] villous surface The condition and function of [illegible] layers is responsible for the fetal metabol[illegible]

The oxygenation and the carbon monox[illegible] take and exchange takes place by simple d[illegible] through the placental barrier (11 13) Th[illegible] carbon monoxide content in the fetus depen[illegible] the mother s tobacco consumption will va[illegible] tween 2 5% and 10% (13) The carbon m[illegible] content of the fetal blood is a combination [illegible] cigarette smoking of the mother and the en[illegible] ous carbon monoxide production in the ch[illegible] which the last factor will result in a saturation [illegible] fetal blood 1 8 times as high as that of the [illegible] (13) The fact that oxygen saturation in the [illegible] circulation is low (70% oxygen saturation in [illegible] cal vein and 26% in umbilical artery) mea[illegible] additional tobacco smoking by the mother [illegible] duce the oxygen transport and result in de[illegible] fetal tissue oxygenation (7)

The formation of the broad basement me[illegible] might possibly be regarded as a repara[illegible] due to the low oxygen saturation Similar c[illegible] have been found in the umbilical artery from [illegible] smokers (2)

The broadening of the basement membra[illegible] to date not been described in animal ex[illegible] studies (4 10) It might possibly be due to a s[illegible] human reaction—or to reaction in fetal tissue [illegible]

Recently a report has been published de[illegible] broadening of the basement membrane in t[illegible]

tion (9) This could be a result of the increasing tobacco smoking amongst young people children and teenagers but should perhaps also be explained as a late complication of maternal smoking during pregnancy

ophoblast		
	Loss of cyto- plasm	Basal plasma membrane polymorphism
	–	–
	–	–
	–	–
	+	+
	+	++
	+++	++++
	++++	++++

itas at term (16) The broad basement orane was found to be associated with the fol g disorders prematurity essential hyperten pre eclamptic toxæmia and diabetes mellitus ing of the membrane was seen in connection antigen/antibody reaction elsewhere in the (16) No possible correlation to tobacco con tion was mentioned

addition to the suggested change in the fetal bolism caused by the broad basement brane the essential decrease in vascularisation rovide an obvious decrease in metabolism and ion across the placental barrier These -anatomical changes could explain the fact newborn children of heavy smokers are small

e present study and the investigation of the ilical artery (2) have shown that tobacco smok uring pregnancy is harmful to the fetal tissue would expect similar changes to be found in the orn children Future studies must determine her or not these changes are reversible

nong recent publications dealing with athero- osis there have been reports of atherosclerosis ildhood calcification of the aortic valve sev ases of fully developed acute myocardial in ion in children and the chaotic arteriopathy (5 Whether or not this is due to genetic factors or amage to the fetus during pregnancy is left un uned

iring recent years (1972–1975) several young le (<30 years old) in Denmark have been re ed as suffering from acute myocardial infarc

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CARPAL TUNNEL SYNDROME IN OVARIECTOMIZED WOMEN

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act Electrophysiological parameters were studied ' gynecological patients before and after major ological surgery No changes in maximal nerve con on velocity or simple reaction time could be found either hysterectomy or ovariectomy Of the 20 ectomized patients 3 developed subjective symp and electrophysiological signs of the carpal tunnel ome within a few months after surgery Thus the l tunnel syndrome which is common in women of ipausal age seems to be precipitated also by enic menopause The present findings indicate that an relaxin overproduction cannot be the basis of the l tunnel syndrome but they are consistent with the that the syndrome is a sign of hypothalamic physeal overactivity or imbalance

maximal peripheral nerve conduction veloci NCV) of women are a little slower than those ien of equal stature if temperature and age aken into account (6) The difference in NCV een the sexes may depend upon hormonal in ices In connection with the hormonal changes ienopause and ovariectomy there might be iges also in some aspects of peripheral nervous tion possibly even causing part of the subjec menopausal symptoms

ie present study was undertaken in order to stigate 1) whether the maximal peripheral nerve luction velocities change as a result of iectomy and 2) whether estrogen therapy has effect on nerve conduction velocity after iectomy As the carpal tunnel syndrome pa s are mostly women in or past the menopause 1) the peripheral nerve segments to be studied chosen so as to reveal 3) median nerve func changes 4) A study of simple reaction time was ided to reveal whether the possible nerve func changes are accompanied by similar changes in ral nervous system functions

METHODS

The 32 subjects were 36–54 (mean 47 1) years old and patients of the gynaecological clinic of the Turku Uni versity Hospital They were all menstruating prior to sur gery They were divided into three groups hysterectomy was performed on twelve patients (Group 1) On twenty hysterectomy and bilateral ovariectomy was performed Ten of the ovariectomized patients (Group 2) received estrogen substitution therapy (2 mg of estradiol valerate pro die) The other ten ovariectomized patients did not receive any therapy (Group 3)

The electrophysiological measurements were made dur ing three examinations on the day before surgery one month after surgery but before the patients in the second group had received any estrogen therapy and finally three months after surgery

The NCV was determined from the beginning of the first negative deflection of the averaged action potentials to 10 percutaneous supramaximal (50 V) stimulations of 0 2 ms duration in five nerve segments The measured NCV s were the sensory antidromic NCV of the right sural nerve at the ankle (3) the sensory antidromic NCV of the right radial nerve at the wrist (4) the sensory antidromic NCV of the right median nerve from the wrist to the base of the middle finger and from the elbow to the wrist (9) and the motor NCV of the right median nerve from the elbow to the wrist The distal motor latency from the wrist to the thenar musculature was also noted

The slowing of the distal sensory latency—here meas ured as the conduction velocity—between the wrist and the middle finger and the slowing of the motor latency from the wrist to the thenar musculature have been shown to be the most sensitive electrophysiological indi cators of the carpal tunnel syndrome (15) A marked de crease of the sensory nerve action potential in the middle finger electrodes to less than 10 uV was also noted as it has diagnostic value in the carpal tunnel syndrome (5)

Neurological signs of the carpal tunnel syndrome were also systematically looked for Tinel s sign wrist flexion test hypesthesia in the four radial fingers atrophy of the thenar musculature If a patient complained of severe numbness or pain in her hands electromyography of the hand musculature was performed

The method of the reaction time study has been published elsewhere (7)

Table I *Patients with numbness or pathological findings*

n=numbness of any fingers α=amplitude of median sensory NAP<10 μV β=sensory NCV of median wrist finger<40 m/s γ=median motor latency wrist–thenar<4 75 ms δ=sural sensory NCV<40 m/s radial sensory ... m/s ()=borderline value *=denervation of thenar musculature **=denervation of both thenar and hyp... musculature

Patient	Age (y)	Before surgery	1 month after	4 months after	Diagnosis
Group 1 Hysterectomy only (1?)					
M H	43	n	–	–	None
K U	44	(γ)	–	nα(γ)	None
K L	44	–	n	–	None
H L	48	–	–	n *	CVII–CVIII syndrome?
Group 2 Ovariectomy+estrogen (10)					
L I	41	n	n	n	None
A V	46	n	n	–	None
L L	49	n(β)	nαβ	nαβγ	Probable carpal tunnel syndrome
M P	50	nβγδ	–	–	Polyneuropathy
Group 3 Ovariectomy only (10)					
S M	47	β	–	–	None
M S	48	n	n	nαβ	Carpal tunnel syndrome
T K	50	n	–	nαβγ	Carpal tunnel syndrome
I P	50	n	n	n	None
A A	54	n	n	nα**	CVII–CVIII syndrome?

RESULTS

There were no significant differences either between the three patient groups or between examinations 1 2 and 3 in any measured NCV or a patient s calculated mean of all five NCVs (two way analysis of variance and *t* tests) Correction of the NCVs on the basis of skin temperatures over the nerve seg according to an unpublished method from laboratory did not change these results Nor did the reaction time study give any significant differences between examinations or patient groups

However seven patients complained of increased numbness in their hands at some examination after the surgery Of these three showed slowing of the wrist middle finger sensory NCV or delayed median nerve distal motor latency The findings of all patients with complaints of numbness at any examination or with at least one pathological electrophysiological measure are combined in Table I The values of the measures considered pathological in the table are taken from (3 4 9 15) The diagnosis in cases where it was possible to make one on the basis of the electrophysiological and clinical findings is included (Table I)

In two cases H L 48 and A A 54 the numbness and other findings cannot be ascribed solely to a carpal tunnel syndrome as both pat... electromyographic denervation of both hypothenar musculature A radical sy... gests itself as they also had some neck pain ... 50 had generally slowed NCVs and also c... tremities on examination 1 The etiology wa... ably severe anemia After blood transfusio... had no symptoms or signs Also S M ... unusually cold extremities on examination ...

Three patients developed a probable ... fledged carpal tunnel syndrome after the ... cological surgery two in the ovariectomy ... group one in the ovariectomy+estrogen gr...

Case 1 M S 48 had had some numbness of he... from time to time for years Before surgery there ... pathological clinical or electrophysiological ... neither were there any on examination ? Three ... after the ovariectomy she had increased numb... also some night pain in her hands Decrease of a... and slowing of the distal median sensory NCV ... with a positive Tinel s sign and denervation of th... musculature were the grounds for the carpal tun... drome diagnosis in her right hand She did not ... more surgery was content with only analgesi... and the symptoms have declined to their for... over 1 5 years She has had similar symptoms ... hands

2 T K 50 had sometimes had slight numbness of hands before surgery One month after the ectomy she was perfectly all right Three months the surgery numbness of her right hand disturbed eep Decrease of the amplitude of the sensory nerve potential in the middle finger and slowing of the sensory NCV and the motor distal latency of the *median nerve with no other NCV changes indicated a* l tunnel syndrome Two months later she had very e left hand pain denervation in her left median the musculature and found much relief from a left side verse carpal ligament discision In the right hand the toms also increased and about half a year after the and operation she had one also on the right side with effect for a few weeks Slowly returning pain indi that the right side operation has been a partial fail

3 L L 49 had had some night numbness of her for years On examination 1 her median distal ry NCV was slow the borderline value On exami 2 the numbness had increased and the median ry distal NCV was definitely slowed and the cor nding amplitude decreased On examination 3 the motor latency of the right median also was slowed the subjective symptoms had decreased somewhat wards she has had three periods of very severe night ness and burning pain in her right hand but has ed no other therapy than analgetics as the symptoms decreased by the time she has sought medical advice *mptoms in the left hand*

other patient in the ovariectomy+estrogen had symptoms and findings suggestive of a l tunnel syndrome on examination 2 but not amination 1 She is not included as her symp- and findings were on the left side only and no presurgery measures were determined in ffected hand Her symptoms subsided almost letely by examination 3

e patient K U 44 in table I has also some ngs indicating median nerve dysfunction but ymptoms and clinical signs were so slight that finite diagnosis could be made

DISCUSSION

nerve conduction and reaction time findings ate that changes in these types of nervous em functions which are large enough to be ured by our methods do not occur after ectomy at least not within a few months The ence between the NCVs of men and women does not seem to depend on ovarian hormones

e finding does not exclude the possibility that nerve conduction changes in slow myelinated or unmyelinated fibres form a part of the mechanism underlying postmenopausal symptoms

Of the 32 patients at least 2 and probably 3 developed a carpal tunnel syndrome in one or both hands after major gynaecological surgery Ovariectomy had been performed on all of these patients Thus one of ten patients developed the carpal tunnel syndrome after ovariectomy The full fledged syndromes developed in patients that received no estrogen substitution therapy but the differences between the patient groups are of course not statistically significant There are no studies on the incidence and prevalence of the carpal tunnel syndrome in an unselected population of 40–50-year old women For comparison may be mentioned that by similar electrophysiological means Leven & Huffman (8) found the carpal tunnel syndrome in one out of 48 diabetic patients and one out of 53 normals The carpal tunnel syndrome is considered to be fairly common in diabetics (11)

Thus the present findings indicate that it is well worth while to check for symptoms of the carpal tunnel syndrome in women of menopausal age especially after iatrogenic menopause The cause of insomnia numbness and pain in the hands may be this syndrome whose surgical cure is simple and effective

The present findings also have some bearing on the etiology of the carpal tunnel syndrome The pathophysiological mechanism of the syndrome is compression of the median nerve by the transverse carpal ligament (11) Anatomical anomalies of the median nerve or abnormalities of the wrist or after trauma or in rheumatoid disease may be etiological or predisposing factors (11) However they can hardly explain the great preponderance of women (women to men 3 1) and especially of women of menopausal age (1 11) This fact suggests the importance of female hormonal function or dysfunction for the development of the syndrome especially as it very often is bilateral

As the syndrome also is common in pregnant women (1 7) it has been suggested first by Wilkinson (16) that excess ovarian relaxin production may be the decisive factor The fact that our patients developed the syndrome after ovariectomy seems to rule out this possibility

Estrogen has been shown to have some therapeutic value in the carpal tunnel syndrome (7 13) but contraceptive pills have been considered a cause

(12) Our results are of course inconclusive as to the effect of estrogen

Our results are consistent with an indirect effect of estrogen or other ovarian hormones (13) The loss of ovarian hormone production may cause hyperactivity or imbalance of the hypothalamic hypophyseal system not only of FSH and LH but possibly of other hormones as well at least in some women The role of STH or similar hormones like human placental lactogen in pregnancy and possibly even prolactin is suggested by the fact that the carpal tunnel syndrome is common almost the rule in active acromegaly (10)

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ABNORMAL URETERAL PERISTALTIC ACTIVITY DURING PREGNANCY

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…t Ureteral peristalsis in five pregnant patients …ms of acute renal outflow obstruction was studied … aid of a new technique for recording intraureteral (ureterometry) With this technique it is possible …d the intraureteral pressure at three different … the ureter simultaneously The rate of propaga… direction of the peristaltic waves can thus be …ed Retrograde peristalsis was found in three of … patients and in one patient no peristaltic activity …ent at all The fifth patient demonstrated normal …le peristalsis The findings at renography in the …age were in accordance with the ureterometric

…nsport of urine from the renal pelvis to the … bladder is due mainly to ureteral peristalsis …omenon which is of great interest to the …ologist It is well known that pregnancy as … tumours of the reproductive organs can in… with the transport of urine by compressing …ter (3 4 7 9 10 14 15) However ureteral …on characteristic of pregnancy may also be … the effect of progesterone and the effect on …ay not be due solely to extrinsic pressure

…teral activity is usually studied with uro… This method however gives only instan…is pictures of ureteral function Cineradio… of the ureters gives more detailed informa… ureteral peristalsis but opinions differ on the …onal significance of such information (5 6 …urthermore such an investigation technique …t be used during pregnancy

…teral peristalsis can also be studied for a … time with the aid of intraureteral pressure …dings (5 6 10 11) Such investigations have …o been performed with a conventional ure…catheter connected to a pressure transducer …ver when using only one catheter the intraureteral pressure is recorded at one level only and no information about the pressure amplitudes at other levels of the ureter is obtained Hence it is not possible to calculate the direction and propagation rate of the peristaltic waves In addition the use of a conventional ureteral catheter with a side hole involves also the risk of the ureteral mucosa plugging the aperture of the catheter with an incorrect recording as a result (5 6 12)

To avoid these disadvantages a new technique for recording intraureteral pressures (ureterometry) has recently been devised (12) With this technique it is possible to determine the rate of propagation and direction of ureteral contractions along the ureter

In a ureterometric study of healthy women with this technique it was observed that the normally antegrade direction of ureteral peristalsis was sometimes transiently (< 1 min) reversed (12) These short episodes of retroperistalsis were not accompanied by any discomfort to the patients In a following study of the ureters with combined cineradiography and ureterometry it was noted that longer periods of retroperistalsis (>15 min) sometimes occurred in patients with genital tumours (15) The peristaltic waves then travelled towards the kidney and prevented the urine from reaching the bladder This resulted in a functional ureteral stasis with a high intrapelvic pressure and the patients then complained of pain in the flank (15)

Ureteral dilatation is a common phenomenon in pregnancy In most cases it is asymptomatic In some patients however it is combined with episodes of severe pain in the flank In the absence of mechanical obstruction such as ureteral stones the cause of combined ureteral stasis and suddenly marked pain is obscure It was therefore thought to

Table I *Relevant data of the five investigated patients*

Pat No	Age	Month of gestation	Renography	Side of pain
1	28	Pregnant mens VIII	Obstruction right normal left	Right flank
2	26	Pregnant mens VI	Obstruction right normal left	Right flank
3	29	Pregnant mens V	Obstruction right normal left	Right flank
4	28	Pregnant mens VII	Obstruction right normal left	Right flank
5	32	Pregnant mens IX	Normal bilateral	Both flanks

be of interest to perform a ureterometric study in pregnant patients admitted to the hospital because of pain in the flank due to suspected acute renal obstruction The question was whether retrograde ureteral peristalsis was common in these patients

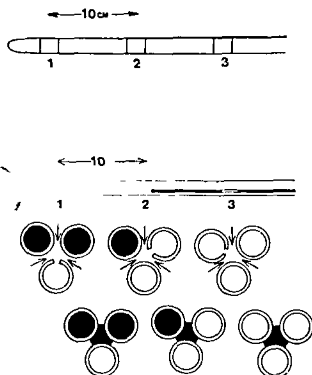


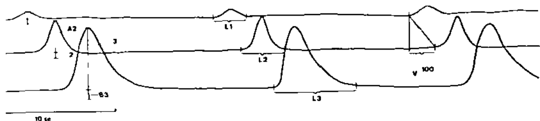
Fig 1 Catheter used for transmission of intraureteric pressures Pressure is transmitted from three points 1 2 och 3 which are 10 cm apart The lower part of the figure shows cross sections of the catheter at every recording section and between these sections The black colour indicates glue Note the possibility for urine to flow into the measuring aperture of the relevant channel Due to the construction of the catheter ureteral mucosa cannot interfere with the measuring aperture

MATERIAL

Five pregnant patients in the fifth to ninth m pregnancy were examined (Table I) All pa pregnant for the first time and all denied from the urological tract The pregnancy cated until the appearance of the actual sy admitted to the hospital all patients complained flank pain which had continued for some hours cases the pain was also combined with dysuria patients were examined no complications from the the uterus were found Microscopic examination urine revealed nothing remarkable No fe During the examination the most striking the marked tenderness in the right flank in four of patients The preliminary diagnosis was in all fi acute renal obstruction and the patients were re acute renography Due to the result of this inve (Table I) and to the severe pain—in some patie unlike renal colic —it seemed justified in a perform a cystoscopy including passage of catheter in order to exclude mechanical obstr study ureteral peristalsis at the same time a cording catheter was used instead of a conven teral catheter

Recording technique

The ureterometric investigation technique has scribed in detail elsewhere (12) It is therefore o outlined here The intraureteral pressure was re means of a specially designed multichannel cat 1) connected to pressure transducers (Elem 741) After amplifying (Elema Siemens EMT pressure signals were recorded by an ink je (Elema Siemens 81) As the intraureteral pre recorded at three levels simultaneously it was different levels of the ureter not only to cal intraluminal pressure amplitudes caused by th contractions but also to determine the rate and d the peristaltic waves Fig 2 gives a normal in pressure diagram obtained with this recording The calibration procedure which included no pressure transducers but also the recording c described elsewhere (12)



Normal ureteral contractions recorded at three : levels in the ureter 1 2 and 3 A=amplitude cm ·basal or resting pressure cm H_2O L=duration of ion sec V=rate of propagation mm/s The up- tracing gives the intraluminal pressure at the uppermost part of the ureter near the renal pelvis the middle tracing at the middle part of the ureter and the bottom tracing at the terminal part of the ureter As a rule the recordings are made 25 15 and 5 cm from the urinary bladder respectively

ental procedure

: aid of a Wolff ureterocystoscope the recording was placed in the ureter with the tip of the cathe e renal pelvis This excluded mechanical obstruc e lowermost recording section of the catheter was iced 5 cm from the ureteral orifice This means ing to the construction of the catheter (Fig 1) the teral pressure was recorded simultaneously 5 15 cm from the bladder During the recording the was empty The ureterometry was undertaken on e described by the patient as painful and showing in the renogram (Table I) When possible metry was also undertaken on the other side er some of the patients complained of severe pain these cases the investigation could not from an point of view be prolonged to include also the ted side The recordings covered 20–30 minutes 'ere not repeated as repeated pas age of a catheter : ureter would presumably have increased the risk ary infection especially in these patients All pa 'eceived antibiotics ampicillin 2 g daily for 14 days cillin Astra Sweden) Renography was done and :ultured immediately before and several times af : recording procedure

'ions and interpretations of the records

ppermost tracing of the pressure diagrams (Figs 'as recorded by means of the uppermost pressure ing section of the catheter (Fig 1) As described this part of the catheter was placed 25 cm from the al orifice and was thus situated just below the renal

The middle and the lowermost tracings were ed from the middle and the lowermost pressure ns of the catheter thus presenting the pressures from iddle and lower part of the ureter respectively The tude of the pressure change is the difference between 'ak pressure observed during the ureteral contraction ie resting pressure between these contractions The if propagation (V mm/sec) is determined from the taken for the contraction wave to travel from one of recording to the next The direction of peristalsis grade or retrograde) can be determined by observing at which point of recording the contraction wave first appears The frequency (F) is the number of contractions per minute

RESULTS

Table I gives the results of the renographies done in the acute stages Except for patient 5 all renograms demonstrated obstruction on the affected side

From Table II which gives the ureterometric data from the patients it is clear that retrograde peristaltic waves were present in three of the five patients The retroperistalsis persisted in these pa tients throughout the recording period (>20 min) Figs 3 *a* and *b* give pressure recordings from one of these patients (no 1 Tables I and II) Fig 3 *a* demonstrates that extensive retrograde ureteral peristalsis was present on the right side whereas Fig 3 *b* shows normal antegrade peristalsis on the left side As can be seen from Table I the renogram in this patient demonstrated ureteral stasis on the right side but not on the left

The resting pressure i e the basic pressure be tween contractions were higher at all recording levels in the abnormal right ureter compared with those in the normal left The most striking dis crepancy in this respect was present at the highest recording level near the renal pelvis where the resting pressure was almost three times as high in the right ureter as in the left The patient also com plained of pain in the right flank (Table I)

The rate of propagation as well as the peristaltic pressure amplitude at different recording levels was about the same as those given previously (12 15)

The ureterometric findings in patients 2 and 3 (Table II) were about the same as those

Table II *Ureterometric data of the five investigated patients*

Pat No	Ureter examined	V=peristaltic travel rate (mm/s)	F=contractions/min	Direction of peristalsis	Peristaltic pressure amplitude and (Resting pressure) in cm H_2O at distances from bladder indicated 5 cm	15 cm
1	Right	40	7	Retrograde	30 (10)	25 (15)
	Left	30	4	Antegrade	25 (6)	15 (7)
2	Right	40	6	Retrograde	32 (12)	25 (15)
3	Right	35	6	Retrograde	20 (10)	20 (15)
4	Right	–	–	–	– (15)	– (15)
	Left	30	4	Antegrade	22 (8)	25 (10)
5	Right	35	7	Antegrade	25 (8)	20 (9)
	Left	30	6	Antegrade	28 (8)	20 (9)

sumably because of the lack of a suitable technique for demonstrating the direction of the ureteral contractions When using two conventional ureteral catheters for intraureteral pressure recordings Kul sometimes recorded retrograde peristalsis (5) It has then been claimed that the presence of *two* rigid conventional ureteral catheters (size 5 F) (1 F=0 33 mm) may obstruct the urinary flow and disturb the normal activity of the ureter The present investigation was undertaken with a very thin and flexible catheter Its outer diameter is only 4 F=~1 3 mm It has previously been confirmed with combined ureteral pyelography and ureterometry that this catheter does not produce ureteral stasis in healthy npregnant women (15) If the presence of the ording catheter was the main reason for the re eristalsis it should have occurred also on the naffected side

The retrograde contractions in the present investigation originated entirely from the lower part of the ureter where recently numerous adrenergic and cholinergic nerve-cells have been demonstrated (11) It is conceivable that the activity in these nerve-cells under certain circumstances can influence the automaticity of latent pacemaker cells in this part of the ureter and thereby interfere with the activity of the normal pacemaker cells situated in the upper part of the ureter or renal pelvis In a previous ureterometric investigation before during and after Wertheim hystereotomy it was noticed that retrograde peristalsis occurred during dissection of the lower part of the ureter (13) When manipulating the lower part of the ureter in dogs Enhorning & Weaver also elicited retrograde peristalsis (2)

It has previously been demonstrated that episodes of retrograde ureteral contractions duced a functional ureteral stasis When the traction waves travelled towards the kidn prevented urine from reaching the bladder caused a rapid increase in intrapelvic pressur As seen from the ureterometric data (Tabl II intraureteral resting pressures were present recording point close to the renal pelvis in tients with retrograde peristalsis

It is now generally accepted that flank pa renal colic pain in cases of ureteral obstru due to a sudden increase in the intrapelvic pr It is therefore possible that periods of re peristalsis can contribute to the explanation marked pain and pronounced ureteral stasis sometimes occur in pregnant patients In t vestigation only five patients were examined of them may be considered healthy from a cal point of view It is therefore not quite cor compare the ureterometric data of these p with those obtained in normal non pregn unteers (12) For several reasons—above al cal—we have not examined urological healthy nant patients with our ureterometric tech However investigations of pregnant patients out signs of ureteral obstruction have performed by Ruby & Sala (9 10) In the vestigations a conventional ureteral cathe only one measuring aperture was used It questioned whether such a technique perm tain conclusions about ureteral function at d levels in the ureter To do this it is necess perform simultaneous pressure recordings at ent levels in the ureter (5 6 12 15) H

normal antegrade peristalsis was demon
d our data are about the same as those re
by Ruby & Sala (9 10) These authors sug
d that the dilatation of the ureters during
ancy is due mainly to mechanical obstruction
of the results of this investigation may also
r this suggestion For it has been claimed that
rst sign of mild ureteral obstruction is an in
in the resting pressure and frequency of con
ons (1 2 5 15) In this investigation also in
women with normal antegrade peristalsis the
g pressures were higher and the frequency of
actions increased compared with those re
d in healthy volunteers (12)

management of pregnant patients with seri
reteral stasis is delicate The passage of the
ding catheter into the renal pelvis in our pa
excluded mechanical obstruction The pa
were then treated symptomatically with
erine 80 mg/day (Papaverine ACO Sweden)
hey were instructed to lie on the unaffected
All patients were free from their acute pain
1 20 hours
w renograms after one week demonstrated re
on of the obstruction on the affected side
ver the renograms were not normal until two
is after the delivery All five patients were
red at full term without any complications
raphies obtained from all the patients two
is after the delivery were normal There were
ms of urinary infection in these patients as the
microscopy as well as repeated urine cultures
normal However all the patients were given
otics During the first 14 days after the exami
1 the women received ampicillin 2 g/day
acillin Astra Sweden) and in the following
urantoin 1 5 g daily (Furadantin Pharmacia
en) throughout the pregnancy
side effects of the ureterometric investiga
were noticed It must however be em
zed that passage of a catheter into the ure
ways involves risks One must therefore have
ct indication for such a manoeuvre and in our
on the patient should receive antibiotics during
fter this procedure
ray examinations should be avoided during
iancy In suspected ureteral obstruction pas
of a catheter into the ureter might therefore
times be necessary In such a situation it is
rtant to collect as much information as possi
bout ureteral function The present recording
catheter seems superior to conventional ureteral catheters It gives information not only on the presence of a mechanical obstruction but also detailed information about ureteral peristalsis

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CYCLIC FLUCTUATION IN NORADRENALINE TRANSMITTER OF THE MONKEY OVIDUCT

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Cyclic variations in noradrenaline of the sym nerves (short adrenergic neurons) innervating ooth musculature of the oviduct have been deter by fluorescence histochemistry and fluorometric ements in monkeys (Macaca mulatta) During the ry phase there is more than twice as much neuronal naline in the oviduct compared with the prolifera ase This suggests that the system of adrenergic in the primate oviduct is involved in the motility s associated with alterations in the level of en us estrogen and progesterone during the menstrual

nerally believed that the smooth musculature oviduct plays an important role in the trans the ovum from the ovary towards the uterus e detailed mechanisms involved in this com nction are not very well understood (24 33) is much experimental evidence to indicate ie motor activity of the tubal smooth muscu is under adrenergic influence mediated receptors associated with excitation and β ors which are inhibitory (3) Under the in e of hormones there is a functional balance en these receptors so that in essence en potentiates the α receptor response as the response to β receptor stimulation is sed by progesterone (13) Fluorescence hemistry has demonstrated that the oviduct es a well-developed adrenergic innervation related to the smooth musculature (26 30) the activity of the adrenergic nerves in the t can be affected by sex steroids administra estrogen has been found to increase the level al noradrenaline which becomes normalized the influence of progesterone given along he estrogen (30)

The present study on monkey oviducts was undertaken to find out whether such fluctuations in the noradrenaline transmitter can be revealed also during the normal endogenous hormone changes associated with the menstrual cycle

MATERIAL AND METHODS

The material consisted of 13 adult normally menstruating rhesus monkeys (Macaca mulatta) The cyclic stage was determined in either of the following ways (*a*) relation to the first day of last menstrual bleeding (*b*) histological examination of the endometrium (formalin fixed material stained in hematoxylin and eosin) and (*c*) daily radioimmunoassay of estradiol 17β and progesterone in plasma (10 37) One or both oviducts were removed during nembutal anaesthesia For the fluorescence histochemical demonstration of noradrenaline (2) two of the tubes also containing the tubo-uterine junction were used for serial sectioning Only small pieces from the isthmus 2 cm from the tubo uterine junction were taken from the remainder of the oviducts The tissue pieces were frozen to the temperature of liquid nitrogen freeze-dried treated with formaldehyde gas at +80°C for 1 hr sectioned at 6 μ and mounted in Entellan (Merck) for fluorescence microscopy (2)

Apart from the small pieces taken for the histofluorescence examinations the whole oviducts from 11 of the animals were homogenized in 0 4 N ice cold perchloric acid for chemical determination of noradrenaline (1 12) Either one or both oviducts were used in each determination

RESULTS

In all parts of the oviduct fluorescence microscopy showed the presence of numerous adrenergic nerve terminals emitting a green light under the optical conditions used (2) and characterized by a beaded

ıcts obtained at day 19–26) having a mean of 100 pg/ml The mean plasma progesterone ntrations were low in both groups 0 4 and 0 2 respectively The concentration of nor aline during the secretory phase was signifi y higher (Student s *t* test $0\ 001<p<0\ 01$) than g the proliferation phase For comparison sponding mean noradrenaline values compiled the material of human oviducts reported by an et al (26) has been inserted in Fig 2

DISCUSSION

reliminary histochemical account of the ergic nerve supply of the human Fallopian was presented in 1964 by Brundin and Wirsen subsequently a *detailed fluorescence histo*ıcal investigation combined with chemical de nations of noradrenaline was performed by an et al (26) Part of the study was repeated confirmed by Kubo et al (14) Fluorescence chemistry of the monkey oviduct reported in resent study as well as by Cottle & Higgs (8) shown an innervation pattern closely resem that of the human oviduct The most promi adrenergic innervation is found in the circular th muscle layer particularly in the isthmus n

the basis of histochemical and functional es in rabbits the presence of an adrenergic ıcter mechanism in the isthmus of the oviduct een proposed (6) Judging from the conspicu high concentration of neuronal noradrenaline ured in this region in the present and previous tudies it is likely that such a mechanism is to und also in the primate isthmus It was noted in human material (26) that the degree of energic innervation was especially pronounced at part of the isthmus nearest the ampulla (26) h may indicate that the isthmus is not function ıniform in its sphincter properties The results ectrical stimulation of perivascular nerves in uman Fallopian tube (20–22) and of transmural stimulation (32) suggest that the histochemi l demonstrable adrenergic nerve supply repre a functional innervation capable of influencing notor activity of its smooth musculature

a addition to the vascular adrenergic nerves the na propria of the mucosa also contained rescent fibres whose destination was not pos to determine in the fluorescence microscope

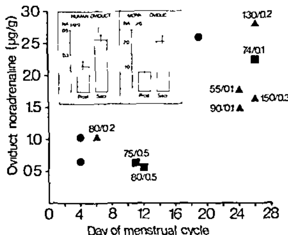


Fig 2 Concentrations of tubal noradrenaline at various stages of the menstrual cycle Each point represents one determination performed on one or both tubes The day of the menstrual cycle was determined from the first day of the last menstruation this was the only parameter used for 3 of the animals (●) In other animals the cyclic stage was secured by radioimmunoassay of plasma estrogen and progesterone alone (▲) or in combination with en dometrial histology (■) The steroid values are given as estrogen (pg/ml)/progesterone (ng/ml) *Insert* The mean noradrenaline (NA) values±S E M of the monkey ovi ducts are compared with corresponding values obtained from human oviducts (5) The differences between the noradrenaline concentrations are significant both in the human ($p<0\ 02$) and monkey ($0\ 001<p<0\ 01$) material

They could for example be related to smooth muscle fibres claimed to exist in this region (23)

The amount and distribution of the adrenergic innervation of the primate oviduct agree with observations in rabbit (6 9 27) cat (34) and dog (29) It is known from the classical studies by Langley & Anderson in 1895–96 that the sympathetic inflow to the oviduct comes by the hypogastric nerve (15–18) Transection of this nerve causes however only a partial reduction in chemically measured noradrenaline in the oviduct (6 25 34) confirming the presence of a peripheral relay distal to the level of transection The adrenergic ganglia forming this relay have been traced by fluorescence microscopy and found to be located in or near the utero-vaginal junction (27 34) where such ganglia have been demonstrated also in humans (26) The chemical determinations following the hypogastric transections showed that most if not all of the adrenergic innervation in the feline oviduct and about one third to one half of the supply to the rabbit oviduct represents fibres belonging to the



Fig 1 Fluorescence photomicrographs of transversely sectioned oviducts isthmus region The majority of fluorescent *adrenergic nerve terminals* run in the circular muscle layer in the same direction as the smooth muscle cells The *number of* fluorescent axon terminals visible during (*a*) the secretory phase of the menstrual c much larger than (*b*) during the proliferat agreement with the chemical det noradrenaline (cf Fig 2 insert) ×125

arance Most of the fibres were distributed in association with the smooth muscle cells ose *direction they* followed in the circular and longitudinal layers The remainder of the fluores *cent nerves* ran along vessels both in the muscle layers and in the lamina propria of the mucosa In *addition* the lamina propria contained some adrenergic nerve terminals without clear relation to blood vessels

In the serially sectioned material it could be *shown that* in the ampulla the thin muscle layer received only relatively few adrenergic nerves The *number of fluorescent* fibres showed a distinct in *crease in* the isthmus where the prominent circular muscle layer was particularly well supplied (Fig 1) *The number* of nerves in this layer was maintained *throughout* the entire length of the isthmus The picture was similar also in the tubo-uterine junc *tion* whereas the smooth musculature in the adja *cent* part of the uterus had a lower density of adrenergic nerves compared with the isthmus

On the basis of microscopic analysis of sections from the isthmus it was possible to d strate a clear cyclic variation in the fl microscopic picture of the adrenergic most evident in the circular smooth muscle Thus during the proliferation stage the num fluorescent nerve terminals was moderate a fluorescence was less bright than during the tory phase when the fibres were in add numerous (Fig 1) With regard to the fairly time periods involved it is conceiv bl th does not represent a true variation in the num adrenergic nerves but rather a chan e noradrenaline concentration of the individ ons which means that the transmitter level low for histochemical detection in many nerves during the proliferative phase

As shown in Fig 2 oviducts from the pr tive phase were obtained at cyclic day 4-1 mean plasma estrogen in this phase 78 p somewhat lower than during the secretor

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THE SUPPRESSION OF PUERPERAL LACTATION WITH BROMOCRYPTINE

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ict The therapeutic value of 2-Br-α-ergocryptine for ppression of puerperal lactation was studied in 30 l women 16 received the drug 14 were controls In omen plasma levels of FSH oestradiol and alpha umin were measured in labour and in the early num Brom-ergocryptine was found effectively to ss milk production and alleviate breast pain and stion with no side effects and minimum rebound on The inverse relationship between prolactin and levels reported elsewhere in non-pregnant women ot appear to occur in the early postpartum period ugh there was a significant rise in alpha-lactalbumin in labour and the puerperium over non-pregnant there was no difference between lactating and non ng women

recently attempts to inhibit lactation were lim- to mechanical compression of the breasts restriction of fluid intake supplemented by tic agents which are ineffective and hormonal ition by oestrogens either alone or in combina with progesterone and androgens which were effective but found to increase the risk of ibo-embolic complications in the puerperium earch for a non hormonal compound specifi- inhibiting prolactin release and suppressing ion led to the selection of the ergot alkaloid α-ergocryptine (CB 154)

rlier studies on animals by Fluckiger & Wagner emonstrated the inhibition of lactation by o-ergocryptine Based on these findings the was used by Lutterbeck et al (8) Besser et al nd others for the treatment of non-puerperal torrhoea and by Varga et al (15) Rolland et 11 12) and others for the suppression of oeral lactation

e present study of 30 women was undertaken valuate the clinical effectiveness of Bromo-ergocryptine in suppressing lactation and to observe any side effects over a period of 28 days In six women three on the drug and three controls the plasma FSH and oestradiol levels were estimated as a measure of the effect of the drug on pituitary ovarian function since it has been demonstrated that in the non-pregnant individual there is an inverse relation between prolactin and gonadotrophin secretion (2) Estimation of plasma lactalbumin levels was used as an additional parameter of mammary gland activity (6)

METHODS AND MATERIAL

Women who elected not to breast feed were selected antenatally after the 36th week of pregnancy The plan of study was explained to them and a signed consent obtained only women who had a normal pregnancy and a vaginal delivery were included Special note was made of any concomitant treatment with diuretics phenothiazines or steroids because of the possible effect of these drugs on lactation No alternative methods to suppress lactation were adopted and analgesics were given if required

Women were selected and the tablets allocated double blind except in the six women who volunteered to have blood samples taken who were selected by the statistician controlling the trial to give three in each group In the remaining women the code of the group was not revealed to the investigators until the study was completed Each active tablet contained 2.5 mg of the active compound 2-Br-α-ergocryptine Two tablets (5 mg) were given daily after the main meal usually at midday for the first two weeks and one tablet (2.5 mg) daily for the third week Treatment began within twelve hours of delivery The efficacy of suppression of lactation was assessed by observation of milk production congestion and pain in the breasts or arbitrary scales similar to those described by Rolland & Schellekens (12) (Table I)

Assessment was made at the same time each day based on subjective evaluations by the women who were instructed and supervised by a Research Sister d

Table I *Determination of mammary activity*

Score	Milk production by palpation	Congestion	Pain
0	No milk	Absent	Absent
I	Some drops	Mild	Mild
II	Slight outflow	Moderate	Moderate
III	Stream of milk	Severe	Severe

Requiring analgesics

stay in hospital The observations were entered on score cards which the women maintained for a period of 28 days after delivery and which were then returned in self addressed envelopes Women were finally assessed at the post natal visit six weeks after delivery All general practitioners were requested to inform us should they be called upon to treat any side reactions or if the drug was discontinu d due to other medication

In the six women who volunteered for detailed hormone studies 10 ml of heparinised blood was collected in the first stage of labour after the third stage of labour and on alternate days while they were in hospital Plasma FSH oestradiol and alpha lactalbumin was estimated by radioimmunoassay FSH was assayed by the double anti body radioimmunoassay method of Reuter Gaspard and Franchimont (10) using the FSH Kits produced by CEA IRE SORIN The reference standard for FSH used was of pituitary origin supplied by Calbiochem Its biological po tency is 3 500 IU/mg (IRP2 HMG) Equivalence of refer ence standard/International standards −1 mg Reference Hormone=169±19 mg LER 907 or 2830±370 IU 68/39 MRC Mill Hill

Plasma oestradiol was assayed by the method described by Bolton & Rutherford (3)

Plasma alpha lactalbumin was measured by a double ody radioimmunoassay using antisera raised against ied human alpha lactalbumin prepared by the method arman (1) This material was also used for radioiodina ion and for assay standards

RESULTS

A total of 44 women were recruited Eight were lost sight of and failed to return their cards in six others treatment was discontinued for various reas related to the use of the drug Thirty wome pleted the study 16 on bromo-ergocryptine a controls Complete records were maintained women during the first two weeks two wome not complete the record in the third week seven women on the drug and six controls f maintain the cards in the 4th week The re were rechecked with the women at the pos visit

Statistical analysis of the effect of the d milk production breast congestion and pa judged by the proposition with negligible sig given in Table II Table III shows the propo with more severe symptoms

Moderate to severe pain was noticed in 79 controls as against 19% of patients trea ed Bromo ergocryptine in the first week No pain reported after the second week in women with the drug

No adverse reactions or side effects observed in either group At the postnatal ass ment six weeks after delivery menstruation re established in 5/9 women on the drug and women on the placebo Eleven women fa keep their hospital postnatal appointment currence of lactation was reported by one w in the bromo-ergocryptine group who devel galactorrhoea six weeks postpartum and one after menstruation was re established but regressed without further treatment

Plasma was obtained from six women three trols and three on the active drug Levels of FSH oestradiol 17β and alpha lactalbumin given in Table IV and in Fig 1 the alpha bumin results are compared with the results lactating women The mean alpha lact level in a non pregnant non puerperal group found to be less than 10 ng/ml

Table II *Proportions of subjects with total weekly score equal to 0 or 1*

Week	Milk production		Congestion		Pain	
	Active	Placebo	Active	Placebo	Active	Placebo
1	12/16 75%	1/14 7%**	13/16 81%	1/14 7%	13/16 81%	3/14
2	12/16 75%	2/14 14% *	14/16 88%	6/14 43%	14/16 88%	11/14*
3	14/15 93%	6/13 46%*	15/15 100%	13/13 100%	15/15 100%	11 [illegible]
4	9/9 100%	3/8 38%	9/9 100%	8/8 100%	9/9 100%	7/8 [illegible]

* Statistically significant $P<0.1$ * Statistically significant $P<0.5$

ough a marked increase in alpha lactalbumin were observed in labour and the puerperium does not appear to be any systematic differ in levels observed in lactating and non ng women although those in women on -ergocryptine tend to be somewhat lower umber of cases studied is too small for ical analysis

DISCUSSION

rlier studies of bromo-ergocryptine side ef like heartburn anorexia vomiting and ntestinal symptoms were reported (2 3) but study bromo-ergocryptine has been shown to ctive in suppressing lactation without ill ef In addition the dose schedule over a period of weeks—5 mg daily for the first and second and 2 5 mg daily for the third week almost ated the problems of rebound lactation re l in earlier publication

inhibitory effect of bromo ergocryptine in ssing prolactin release in the galactorrhoea orrhoea syndrome and in puerperal lactation l documented Rolland et al (11) demon d that prolactin concentrations were effectively reduced by bromo-ergocryptine after delivery and FSH was scarcely detectable during late pregnancy and the early postpartum period Our findings of negligible levels in the first ten days after delivery are in agreement The high levels of oestrogen characteristic of pregnancy were seen in samples obtained in early labour and soon after the third stage but showed the usual dramatic fall within 48 hours of delivery to low levels which were maintained through the first ten days in both groups of women The inverse relationship between prolactin and FSH observed in the non pregnant women (2) does not appear to relate to the early post partum period as is evident by a failure in FSH levels to rise after prolactin suppression by bromo-ergocryptine These findings are confirmed by Del Pozo et al (4) who demonstrated a significant in

Table III *Proportion of patients showing moderate to severe pain (scores 3 and 4)*

Week	Active		Placebo	
I	3/16	19%	11/14	79%
II	2/16	12%	3/14	21%
III	0	0	2/13	15%
IV	0	0	1/8	12%

IV *Plasma levels of FSH (ng/ml) oestradiol 17β (ph ml) and α-lactalbumin (ng/ml) in 3 treated and ated women*

r in parenthesis denotes the score for milk production

	Early labour	Third stage	48 hrs	96 hrs	144 hrs	192 hrs	
o							
	0 25	0 27	0 ?5	0 25			
diol	44 000	29 200	37 5	40 5			
bumin		37 (0)	22 (0)	25 (1)			
	0 ?0	0 ?4	0 23				
diol	16 600	8 ?00	104				
bumin		220 (0)	190 (0)				
	0 26	0 1	0 1	0 1	0 ?6	0 25	
diol	28 400	12 200	91	40	22	2?	
bumin	?55 (0)		243 (2)	>300 (2)	>300 (2)	2?0 (1)	
	0 5	0 ?6	0 ?8	0 25	0 26	0 23	0 52
diol	49 000	34 700	590	6?	34	43	
bumin		180 (0)	10_ (0)	71 (0)	140 (0)	>300 (0)	
	0 5	0 ?4	0 25	0 25			
diol	6 600	4 600	37	29			
bumin	36 (0)		13 (1)	10 (1)			
	0 ?5	Too low	Too low	Too low		0 25	
diol	Not done						
bumin	Not done						

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SHORT COMMUNICATION

IN VIVO SUPPRESSION OF UTERINE LYMPHOCYTES DURING EARLY HUMAN PREGNANCY

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immunological acceptance of the foetus being allogeneic homograft is still a perplexing 1omenon How can the foetal trophoblast en into the endometrium and survive while ex d to the maternal immunological defense? It been postulated previously that a mucoprotein king trophoblastic antigens (1) or an anatomi oetomaternal separation (2) should be essential ie engrafting process A number of soluble sub- ces have also been suggested to be responsible his successful transplantation by inhibition of maternal lymphocyte transformation Thus in) studies have demonstrated that human 7onic gonadotropin (HCG) (3–6) human chor somatomammatrophin (HCS) (4) and pro- erone (7) inhibit lymphocyte transformation as iced by different antigens and mitogens In addi tion IgG possibly locally produced eluated from placental tissue has been shown to possess a similar inhibitory effect (8 9) The underlying mechanism is still unclear but these antibodies are most likely not directed towards any as yet specified surface component since antibodies directed against known T or B cell antigens do not significantly inhibit the mitogen induced proliferative response of lymphocytes

During pregnancy a factor has been demonstrated in maternal plasma that suppresses the reactivity of peripheral blood lymphocytes (10 11) As this factor is probably produced by the placenta the lymphocytes adjacent to the uterus should be functionally more suppressed than those in the peripheral circulation

To elucidate this postulation lymphocytes were

ble I Mitogenic response of human lymphocytes from peripheral or uterine blood after 3 days of uring in serumsupplemented cultures (150 000 cells/cult)

		PHA response (mean of triplicates)			Rabbit anti human β microglobulin (mean of triplicates)		
nt	Week of gestation	Peripheral lymphocytes	Uterine lymphocytes	Significance (Student s t test)	Peripheral lymphocytes	Uterine lymphocytes	Significance (Student s t test)
	8	53 416	2 408	$p \geq 0$ 001	6 733	490	$p \geq 0$ 001
	9	110 454	5 8?7	$p \geq 0$ 001	17 709	53_	$p \geq 0$ 001
	9	78 414	60 305	Not signif	14 243	3 659	$p \geq 0$ 001
	1?	30 985	8 606	0 05>p>0 001	2 474	930	Not signif
	9	81 649	58 078	Not signif	13 308	11 509	Not signif
	8	80 438	58 39?	0 05>p>0 001	12 408	4 061	$p \geq 0$ 001
	9	91 510	67 765	0 05>p>0 001	801	4?5	0 05>p>0 001
	9	114 838	9 087	0 05>p>0 001	7 817	3 0 6	0 05>p>0 001
	9	15 997	174	$p \geq 0$ 001	4 669	198	$p \geq 0$ 001

1ythaemagglutinin

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CASE REPORTS

SPONTANEOUS RUPTURE OF THE UTERUS IN THE THIRD TRIMESTER WITH A LIVING FETUS EXPELLED INTO THE ABDOMINAL CAVITY

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From the Departments of Obstetrics and Gynecology (Head P Lundstrom) and Diagnostic Radiology II (Head B Liljequist) University of Umea Umea Sweden

act A case of rupture of the uterus during pre ry with the living f tus expelled intra abdominally is ted The main symptoms were slowly increasing minal colicky pains During the first five days of the tal stay the woman s condition deteriorated and a ytic ileus developed The fetal lie changed between econd and third day from longitudinal to transverse he fetus became situated at the umbilical level At ame time the fetal heart sounds could no longer be ted and the tense uterine wall grew soft The zed fetal lie and the paralytic ileus were radiologi substantiated In spite of a delayed diagnosis the and the mother were both saved The etiology was bly damage to the fundal wall at an earlier curettage ed out because of a spontaneous abortion The dif tial diagnosis is discussed from the obstetrical as well om the radiological and other methodological points w

ture of the uterus during pregnancy or labor is e complication. The incidence mostly reported es between 1 1000 and 1 2500 (3 4 6 10 11 In most cases the rupture seems to have taken e after prolonged labor or to be caused by ob ic manoeuvres

he incidence of uterine rupture seems to be ed to the standard of obstetric care In Uganda d e Short (1958) found an incidence of 1 93 e in Canada Bisson (1947) noted it to be 1354 During a ten year period up to 1974 in our ic 4 cases of the rupture in question were found 8308 deliveries

he present report concerns a case of uterine ure with the living child being expelled into the ominal cavity

CASE REPORT

The woman aged 37 and according to last menstrual period 33 weeks pregnant was admitted because of abdominal pain In 1953 she had had a normal delivery In 1971 she aborted spontaneously in the third month of pregnancy and a curettage was performed with a blunt curette The recovery was uneventful Microscopic examination revealed necrotic chorionic tissue but no villi or myomatous fragments

She had been well until six days before her admission in January 1972 During these days she had experienced intermittent abdominal pain increasing at night and causing loss of sleep

When admitted to hospital her general condition was unaffected and she had no signs of toxemia. The abdomen was soft, with no tenderness The uterine fundus was halfway between the umbilicus and the xiphisternum and its wall was slightly tense The fetus had a longitudinal lie and a cephalic presentation with the head just over the pelvic inlet. The fetal heart rate was within normal limits The cervix was firm and not effaced or dilated and the vagina contained no blood

As premature labor seemed possible Isoxsuprine was administered intravenously The abdominal pain subsided but on the following day the patient—still apparently well and afebrile—complained of stabbing abdominal pain and she occasionally vomited While the uterus was very tense and tender—especially so fundally—and the fundal shape had grown asymmetric the patient admitted insignificant tenderness of the abdomen which seemed soft. Fetal heart rate was ~136 She was given analgesics as well as Terbutalin with some effect.

On the third day after admission the patient had occasionally abdominal pain at infrequent intervals and her general condition was still good There was moderate tenderness in the epigastric region extending further down in the abdomen The uterus seemed as large as before and rather soft. The lie of the fetus had changed to transverse Fetal heart sounds could no longer be detected



Fig 1 Abdominal surveyfilm lateral view High and transverse lie of the fetus surrounded by gas-distended loops of the large and small bowels

During the following two days the symptoms became more severe and in particular the colicky pains The patient grew rather pale She was still afebrile and had normal or slightly elevated blood pressure and a pulse rate of ~100/min The abdomen had become distended and tympanitic Radiological examination of the abdomen beginning on the fourth day revealed a fetus lying transversely at the umbilical level and a severely gas-distended colon (Fig 1) Barium contrast enema failed to disclose a low placed obstruction of the colon (Fig 2)

view of the patient s state and the findings surgical ention was considered necessary The laparotomy that the greatly distended sigmoid concealed the other abdominal organs A small amount of blood was present in the cavity which in its upper part was taken up by the fetus with its head against the spleen The infant was dark blue and had a low muscle tonus the Apgar score being ≤3 The umbilical cord was immediately cut and adequate resuscitative steps taken The infant soon recovered grew pink and started to cry Through a transverse tear of the uterine fundus the placenta was partially expelled (Fig 3) Due to the extensive damage to the wall a subtotal hysterectomy was performed

Microscopically the uterine wall at the side of the rupture showed signs of marked non specific inflammation with degenerative changes of the myometrium No further pathological changes were observed as far as the placenta and uterus were concerned

As regards the child the birth weight being 2600 g and the length 45 cm its arterial blood pH was 6 8 initially The acid base data returned slowly to the normal range So far its development has progressed normally The post-operative course of the mother was uneventful

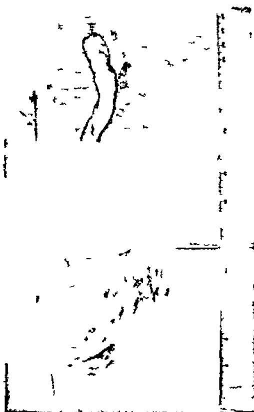
DISCUSSION

The clinical symptoms and signs are plained by the following sequence of increasing uterine activity the tensi part of the fundal wall eventually bro small rupture the edges of which separate slowly Between the 2nd and membranes ruptured Thereafter the f pelled into the abdominal cavity thu lie The uterine activity must then ha considerably and the placenta rema a result of which the uteroplacental kept adequate for nutrition of the fetus tis—and thereby paralytic il uterine contents in the abdominal cavity time of laparotomy the uterine activity causing separation of the placenta which partially expelled through the tear (Fig the utero-placental circulation rapidly bringing about an acute and asphyxia

The radiological signs characteristic of rupture have been described by Zupp Parkinson (1958) and Bishop (1969) but radiologists will probably never encoun unusual but urgent situation more than once recapitulation seems justified with the prese



Fig 2 Survey film about 24 hours after the first 1) frontal view Increased gas distension contrast meal passed through the small bowel cum and ascending colon



3 Frontal view of the subtotally removed uterus nta partially expelled through a tear of the uterine us

classical example The signs are 1) The fetus unexpectedly high in the abdominal cavity 2) fetus does not show the usual adjustment to the ine wall 3) The ordinary uterine shadow is nt 4) Evidence of free fluid may be found in the toneal cavity

the present case points 1–3 were satisfied but e was no evidence of free fluid in the peritoneal ity It seems plausible that the amniotic fluid already absorbed at the time of examination as only a small amount of blood was present at ion not even special procedures could e detected this

he bowel distension in this case indicated some of ileus A mechanical bowel obstruction was luded and consequently the minor paralysis of bowels may have been due to peritoneal irrita Since signs of intestinal dysfunction obscured eral condition the aforementioned four cardinal is may be supplemented with a fifth 5) Signs of alytic intestinal distension

ther *diagnostic methods* could have proven conclusive if available Firstly diagnostic sonar should have demonstrated absence of the amniotic cavity which must be practically pathognomonic as no amniotic fluid was demonstrated in the vagina Furthermore by sonar a reasonably precise estima tion of fetal age can be made which in this particu lar case however is of minor concern Secondly the Doppler effect could have shown that the fetus was alive This would indicate an urgent lapar atomy in case of a correct diagnosis

As far as *differential diagnosis* is concerned certain items were not paid enough attention to particularly the change of fetal lie In retrospect it is apparent from the survey films that the fetus was lying outside the uterus intermingled with more or less distended loops of large and small intestine

It is true that except in labor the real nature of a complication like this will seldom if ever be diagnosed initially in cases where no traumatic manoeuvres are being used and no prior damage to the uterine wall is known of Furthermore in the event of the placenta covering the site of the future rupture acute and probably violent symptoms will occur and be quite different from those of the present case It must however be admitted that in this case with the placenta left in situ for several days after the rupture the diagnosis was unduly delayed The initial suspicion of premature labor is understandable and was partly correct Later a concealed minor abruptio placentae was suspected This too was partly correct This diagnosis how ever should have been abandoned on the third day at the latest

As far as the *etiology of uterine rupture* is con cerned the most common cause in the absence of traumatic manoeuvres is a post-caesarean scar In this case the only possible damage to the uterus is the curettage performed nine months earlier follow ing an early spontaneous abortion This etiology has been suggested e g by Åstedt et al (1967) As the operative report throws no light on this pos sibility and as no myometrial fragments were found on microscopic examination we would merely point out that by use of vacuum aspiration the risk of perforating and damaging the uterine wall with an ovum forceps a curette or a dilator will be avoided And furthermore in an emergency such as heavy bleeding in case of late or missed abortion we think it wiser to empty the uterine cavity digitally by means of a small incision vaginally than to use brisk instrumental manoeuvres



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A CASE OF MASSIVE UNILATERAL OEDEMA OF THE OVARY SIMULATING TUMOUR

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The Central Hospital Holstebro Denmark

act This paper describes the first reported Scan ian case of massive unilateral oedema of the ovary resents the tenth such case in the literature The ible pathogenesis is partial torsion of the mes-ova If suspected clinically such ovaries might be con d

sive oedema of the ovary is a newly recognized copathologic entity The pathogenesis is the as for haemorrhagic infarction from which ive oedema differs in the following respects 1) impairment of venous and lymphatic drainage ot sufficient to cause necrosis 2) the clinical se is not hyperacute 3) the condition is easily aken for tumour 4) the possibility of conserv the ovary and 5) the occurrence of stromal nization with ovarian dysfunction in the more standing cases

he treatment of the nine previously reported s and the present case was total resection ough these ovaries should have been conserved

CASE HISTORY

year-old previously healthy nullipara was admitted a diagnosis of left sided ovarian cyst Menarche at 13½ Menstrual cycle was regular

days before admission the patient complained of intermittent pain in the left iliac fossa Physical nination revealed a normally developed 15 year-old without hirsutism The gynaecological examina revealed a non tender grapefruit sized cystic mass in ower left part of the abdomen Hormonal studies were done At laparotomy the left ovary was found to have n replaced by a somewhat tense tumour The pedicle twisted three times The right ovary was slight enlarged but was not biopsied Left salpingo-horectomy was carried out The postoperative course uneventful

Pathology

The left ovary measured 17½×7×6 cm and weighed 235 g The capsule was intact When cut the tissue was grey white moist with scattered small hemorrhages and several cysts with a diameter up to 1 cm containing clear fluid (Fig 1)

Microscopic sections of the ovary showed oedema most pronouncedly in the medulla and internal cortex whereas the tunica albuginea was only slightly involved The lymph vessels capillaries veins and arteries were dilated showing congestion There was no stromal luteinization (Fig 2)

COMMENT

Nine cases of massive unilateral oedema of the ovary (1 2 3 4 7) have previously been published The condition presents clinically either in an acute–subacute form (7 cases) with intermittent abdominal pain lasting weeks to months including the present case or in a more chronic form (3 cases) without abdominal pain

The most probable developmental factor is partial torsion or kinking of the mes-ovarium compromising venous and lymphatic drainage but insufficient to cause necrosis (2 4)

This concept is supported both by the microscopic picture and by the fact that torsion of the mes-ovarium was found at operation in four cases In no case was there evidence of a previous pathologic process in the ovary which could predispose to torsion of the mes-ovarium

In two of the previously published chronic cases evidence of virilization and stromal luteinization was seen (2 4) One case (3) showed slight stromal luteinization but no virilization In all three cases biopsy of the other ovary showed no pathological changes thereby differentiating the condition from the Stein–Leventhal syndrome complicated by tor



Fig 1 Oedematous tumour like left ovary

All cases were clinically mis-diagnosed ovarian neoplasms The patients were ju… women 13–33 years of age In this age-group ovary should if possible be conserved. As suggested by Kalstone et al (?) one should … suspicion of the diagnosis of massive edema … ovary with the use of multiple frozen-sec… biopsies as well as attempting to secure the ov… a position preventing torsion of the pedicle In … of dysfunction one should perform a wedge … to restore normal function of the ovary In order … evaluate pathogenic factors one should … perform a wedge biopsy of the other ovary

sion Kalstone et al (2) mentioned that stromal luteinization could be a reaction to mechanical stretching of the stromal cells due to oedema analogous to the stromal luteinization and viriliza tion which can be caused by infiltrative primary and metastatic carcinoma of the ovary even though the neoplastic cells themselves are non hormone producing (5 6)

CONCLUSION

Massive unilateral oedema of the ovary caused … partial torsion of the mes ovarium is a recently … scribed cause of sub acute abdominal pain or v… zation in younger fertile women

The condition has in all cases led to total … resection although an attempt should be made … preserve these ovaries

Fig 2 Microscopic section showing oedema of the ov ary Hematoxylin-eosin ×220

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ANNOUNCEMENTS

Secretariat of F I G O
Information received on the following congresses

VI International Congress of Cytology Tokyo Japan May 2–5 1977
Themes relating to cytology
Information for information contact Dr A Meisels Secretary General of the Congress 1050 Chemin Sainte Foy Quebec PG Canada

XI Acta Endocrinologica Congress Lausanne Switzerland June 19–23 1977
Themes relating to endocrinology
Information for information contact Professor J P Felber Secretary General of the Congress Biochimie Clinique Hopital Cantonal Universitaire 1011 Lausanne Switzerland

VI International Congress of Psychosomatic Obstetrics and Gynecology Rome Italy November 13–19 1977
Information for information contact Professor L Zichella Department of OB/GYN Universita degli Studi di Roma Policlinico Umberto I 00161 Roma Italy

An International Symposium on Genito-Urinary Trichomonasis will be held in Paris 8–9 July 1977
For all information please write to Doctor A Fari S I T G U 5 Blvd de Strasbourg 75010 Paris France

The Fifth International Conference on Birth [illegible] will be held in the Queen Elizabeth Hotel [illegible] Canada from 21–27 August 1977
For a complete program please apply to the Se[illegible] c/o Holland Organizing Centre 16 Lange Voorh[illegible] Hague The Netherlands

The Fourth UICC Training Course in Cancer Re[illegible] arranged by the International Union Against Canc[illegible] take place on 4–17 September 1977 in Budapest
For further information write Dr Lászlo Hok[illegible] search Institute of Oncopathology 11?? Budapest Gy str 7 Hungary

The XVI Congress of the Spanish Fertility Soc[illegible]
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THE MYOMETRIAL RESPONSE TO INTRA UTERINE ADMINISTRATION OF $PGF_{2\alpha}$ AND PGE_2 IN DYSMENORRHEIC WOMEN

V Lundstrom

From the Dept of Obstetrics and Gynecology (Head Prof Ulf Borell)
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act Serial recordings of uterine contractility during nt phases of the menstrual cycle were carried out in ysmenorrheic women and in two subjects during the stage of severe dysmenorrheic pain

sensitivity and reactivity of the uterus to intra e administration of small doses of $PGF_{2\alpha}$ and PGE studied A relative insensitivity of the uterus was l in the proliferative phase and around ovulation The s was highly sensitive to the stimulatory effect of in the secretory phase and at menstruation but ibly not more sensitive than in normal women The sponding results with PGE were rather variable in small doses did not induce any response or slight ilation whereas high doses occasionally caused an ition in the secretory phase and during menstruation e results indicate that $PGF_{2\alpha}$ may be a significant r in eliciting uterine hypercontractility and dys rrheic pain Whether the occasional inhibitory t of PGE is of any significant importance in the genesis of dysmenorrhea cannot be stated

e studies on the etiology of dysmenorrhea have 1 focused on the role of the prostaglandins (1 6 Pickles initiated this concept by claiming that er concentrations of $PGF_{2\alpha}$ occurred in the ometrium and menstrual fluid in women with menorrhea than in those not suffering from istrual pain on the basis of a bio-assay method He suggested that the ratio $PGF_{2\alpha}/PGE_2$ was nportance in eliciting menstrual cramps Similar lies have been made by other investigators using radioimmunoassay technique Judging from the e variation in the reported concentrations it ms evident that it is difficult to determine tissue icentrations adequately Nevertheless it is a fact t severe menstrual pain can be completely elimi ed in the majority of cases by the administration prostaglandin synthetase inhibitors

Martin & Bygdeman have studied the sensitivity of the myometrium to threshold doses of $PGF_{2\alpha}$ and PGE_2 administered into the uterine cavity in normal non pregnant women during various phases of the menstrual cycle (9 10) They found a stimulatory effect of small doses of $PGF_{2\alpha}$ and PGE_2 in the proliferative and secretory phases whereas the uterus was relatively insensitive both to $PGF_{2\alpha}$ and PGE at ovulation In contrast PGE_2 resulted in inhibition of uterine contractility during menstrua tion The problem whether the myometrial sen sitivity to $PGF_{2\alpha}$ and PGE_2 is different in dys menorrheic subjects than in normal women has not been studied

The following investigation was performed to analyse the sensitivity and reactivity of the uterus in women with primary dysmenorrhea to intra uterine administration of $PGF_{2\alpha}$ and PGE_2

PATIENTS AND METHODS

Five women with consistent primary dysmenorrhea and regular menses volunteered for the study Four subjects were nulliparous and one had dysmenorrhea even after two deliveries All cases ovulated according to basal body temperature curves and determinations of progesterone in plasma during the secretory phase of the cycle All vol unteers had normal gynecological examination findings A condom was recommended as a contraceptive agent dur ing the course of the investigation and coitus was prohi bited within 24 hours prior to each recording of uterine contractility Reference to the time of recording in this paper is based upon the number of days before (−) or after (+) the estimated date of ovulation

Threshold doses of $PGF_{2\alpha}$ were administered into the uterine cavity in 3 subjects on four occasions during the cycle in the proliferative phase around ovulation in the secretory phase and at menstruation This part of the study comprised 12 recordings

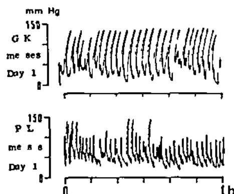


Fig 1 Uterine contractility pattern in 2 patients recorded on the first day of menstrual bleeding and during the period of maximum dysmenorrheic pain Note the high level of uterine tonus and amplitude of contractions

Local administration of PGE_2 was made in 4 women 2 of whom had earlier taken part in the $PGF_{2\alpha}$ treated group In these 2 women recordings were carried out in the secretory phase and at menstruation In the other 2 subjects recordings were made on four occasions in different phases of the cycle Consequently 12 recordings were also made in the PGE_2 group

Two other women were recorded during menstruation in the presence of severe dysmenorrheic pain For ethical reasons prostaglandin was not administered in these cases

Diluted solutions of $PGF_{2\alpha}$ and PGE_2 were prepared from concentrated stocks before each recording session The activity of the stock solution of PGE_2 was tested by ultraviolet absorption following purification on thin layer chromatography and conversion to PGB with alkali before the investigation and after completion of the series of ... There was no evidence of decreased activi... Vials containing the stock solutions were kept deep ... until used The volume of fluid instilled into the ... cavity varied between 0 1 and 1 4 ml Single doses ... 1–10 μg $PGF_{2\alpha}$ were given and the corresponding doses for PGE_2 were in the range of 1–40 μg When high doses of PGE_2 were administered the concentrated stock solution was used

Uterine contractility was recorded by the micro balloon technique The size of the uterine cavity was determined by a probe and the tip of the balloon (capacity 0 1 ml diameter 2 mm length 20 mm) placed approximately one cm below the fundus The catheter was connected to a Statham pressure transducer and a Grass polygraph A thin polyethylene catheter for instillation of the prostaglandin compounds into the uterine cavity had previously been tied to the micro balloon catheter The catheters were kept in position by wedging three gauze swabs into the vagina and around the catheters The basic contractility pattern was recorded for a period of at least 30 minutes before the first injection of $PGF_{2\alpha}$ or PGE_2

A stimulatory or inhibitory response is difficult to measure in the individual case However 19 of the 24 original recordings are illustrated as evidence of the conclusions

RESULTS

The uterine contractility pattern during the ... liferative and secretory phases of the c... similar to that observed in subjects wi... menses During the proliferative phase the ... tractions were characterized by a low amp... and comparatively high frequency Arou... tion there was an increase in frequency an... crease in amplitude During the secretor... there was a gradual increase in ampli... crease in frequency premenstrually devel... more complex or labour like contractions ... the first day of menstrual bleeding and in the ... ence of dysmenorrheic pain the contractility p... was characterized by marked hypertonus h... plitude contractions or frequent complex co... tions without relaxation between them (Fig 1)

Intrauterine administration of $PGF_{2\alpha}$

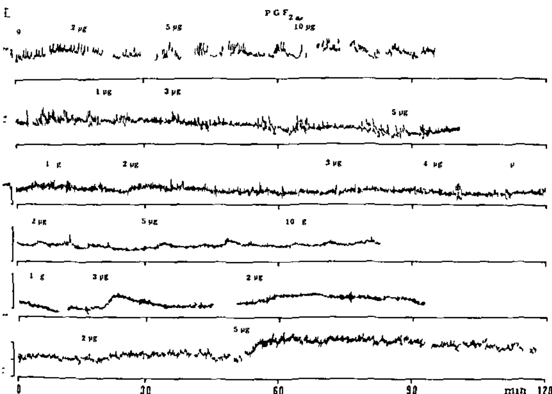
In 3 volunteers studied in the proliferative ... there was no significant response to doses of ... μg $PGF_{2\alpha}$ Of the 3 volunteers studied around ... lation one case did not react to doses up to 10 ... $PGF_{2\alpha}$ while the 2 other subjects responded ... stimulation upon instillation of 2 and 5 μg ... tively (Fig 2)

A marked increase in sensitivity to PGF ... curred during the secretory phase (Fig 2) ... ferent recording sessions in 5 volunteers ... from day +7 to +14 (21st–28th day of the ... Four cases responded with stimulation to ... one volunteer to 5 μg $PGF_{2\alpha}$ The latter ca... corded on day +10 (24th day of the cycle) ... by a rise in tonus of 25 mmHg and an incr... amplitude of 30–40 mmHg (A T Fig 3) Th... ject experienced severe menstrual pain and ... on this rather small dose of $PGF_{2\alpha}$ The ... volunteers obtained moderate menstrual p... one in addition nausea following 5 μg P... similar response was also obtained in one ... on the 4th day of her menstrual bleeding (Fi...

Intrauterine administration of PGE_2

Administration of PGE_2 resulted in a more c... response than that of $PGF_{2\alpha}$ Uterine se... was variable around ovulation one ... reacted to 2 μg PGE_2 another cas... to ... stimulation and a third subject was insensiti... to 30 μg when tested on day −3 and on day ...

In the mid secretory phase there was a d... in uterine tonus in one case following a large...



Uterine sensitivity to local administration of in the proliferative phase and at ovulation of norrheic women

(70 μg) whereas lower doses (2 and 5 μg) had doubtful effects in 2 other volunteers (Fig 4) cases recorded in the late secretory phase d by stimulation following 2 μg and 10 μg ctively (Fig 5)

o recordings were obtained during menstrua it a time when the period of dysmenorrheic had already passed These curves illustrate a small dose of PGE_2 (2 μg) stimulated the actility whereas a large dose (37 μg) signifi y decreased the amplitude (Fig 5)

e patients experienced little or no dys rrheic pain as a result of these injections

DISCUSSION

micro-balloon technique for recording metrial activity has been shown to give identi ecordings as those obtained with the open-end eter method provided that the size of the bal is small (4) Under our experimental conditions ormer method turned out to be more simple and ble than the latter In an earlier study carried out in this department by Martin & Bygdeman con trol injections of physiological saline solution into the uterine cavity did not result in any change in uterine contractility (9) Therefore it was consi dered unnecessary to repeat this type of control study as the technique of instillation and recording was the same in these two investigations The instil led volumes varied between 0 1 and 1 4 ml It is impossible to evaluate the significance of the vol ume factor upon the results However the undi luted stock solutions were administered directly when large doses were given

The basic contractility pattern in the dys menorrheic subjects was approximately the same as that in normal women during the cycle The only difference seemed to be the period of dysmenorrheic pain at menstruation when the uterine tonus and amplitude and frequency of con tractions were consistently high This concept has been controversial for many years but evidence is accumulating in support of uterine contractility and decreased uterine blood flow as important factors in the mechanism of dysmenorrhea (5) It is also a fact

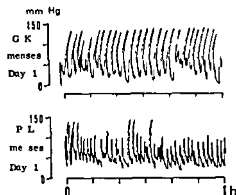


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Intrauterine administration of PGF

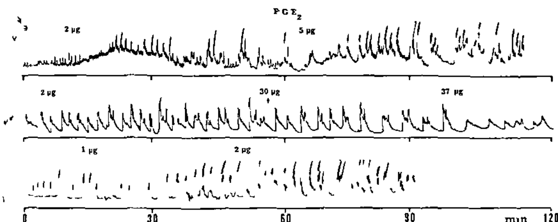
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Uterine response to local administration of PGE_2 in secretory phase and at menstruation Both the a during menstruation were recorded when the period of dysmenorrheic pain had passed Note the stimulatory effect of small doses (G L) and the inhibitory response to a large dose (K H)

e significant relaxation of uterine contractil lowing administration of prostaglandin syn inhibitors or beta stimulating drugs is ac nied by a marked increase in uterine blood and disappearance of dysmenorrheic pain

tin & Bygdeman found that the uterus of il women was highly sensitive to the intra e administration of $PGF_{2\alpha}$ both during the pro ive and secretory phases of the cycle in that a latory response was obtained with doses in the of 1–3 µg A decreased sensitivity was noted peri ovulatory period when doses ranging en 4 and 8 µg did not result in any response e results differ to some extent from those of resent study The uterus did not react to doses or 10 µg in the proliferative phase whereas an ous increase in sensitivity occurred in the sec y phase where all cases responded by stimula of uterine contractility following administration µg $PGF_{2\alpha}$ This means that a significant in se in sensitivity does not occur until the mid or secretory phase and that uterine insensitivity is a particular feature for the periovulatory period lation to the proliferative phase

hether the difference in results between the two lies reflects a difference between normal women dysmenorrheic subjects cannot be answered on basis of available data The uterine response is y variable under the prevailing experimental nditions and the number of experiments in both rtin & Bygdeman s study and the present in tigation is limited There is at any rate an agreement between the two studies that the uterus is sensitive to small doses during the secretory phase and it may be of some interest that uterine sensitivity to $PGF_{2\alpha}$ of dysmenorrheic women in the pre menstrual period is not higher than that of normal women

The period of dysmenorrheic pain during men struation is of course the most relevant time for measuring uterine sensitivity to $PGF_{2\alpha}$ considering the aim of the present investigation For ethical reasons it was not possible to administer $PGF_{2\alpha}$ in the presence of severe pain The presence of an unknown volume of menstrual blood in the cavity resulting in dilution of the injected dose and containing an unknown amount of endogenous prostaglandins may also create uncertainty about the actual effective dose However one recording on the 4th day of menstruation when the stage of uterine cramping and pain was passed illustrates at least that the uterus at menstrual bleeding has a similar sensitivity to that during the secretory phase

In dysmenorrheic women small doses of intra uterine PGE_2 (2–5 µg) either stimulated the con tractility or had no effect at all around ovulation in the secretory phase and at menstruation Large doses (20–40 µg) on the other hand occasionally had a transient inhibitory effect The latter response was observed both in the secretory phase and dur ing menstruation which is in agreement with results obtained in *in vitro* experiments with human myometrial strips (3) Approximately the same re sults were obtained in non-dysmenorrheic women

in *in vivo* studies by Toppozada et al and by Martin & Bygdeman (14 10) The former authors found that the inhibitory response could be elicited in post menopausal women and in one case during the secretory phase of the cycle but only following very large doses (200–300 μg) Moreover the ingestion of contraceptive pills caused a reduced uterine sensitivity to prostaglandin (15) This is of interest considering the fact that oral contraceptives eliminate or reduce dysmenorrheic pain Martin & Bygdeman observed the inhibitory effect of PGE_2 only during menstruation

These results are in contrast to the finding that intravenous administration always results in stimulation irrespective of dose and phase of cycle (11) Another difference between local and systemic administration of prostaglandins relates to the threshold dose levels Ten to twenty times higher doses are needed if the compound is given as a single intravenous injection than if the substance is injected directly into the uterine cavity This may be due to the rapid inactivation process of prostaglandins in the circulation and the lack of inactivating enzymes within the uterus (7)

The relative significance of PGE_2 in the pathogenesis of dysmenorrhea is in this context still obscure since the compound apparently both increases and decreases uterine contractility However judging from the present results it seems robable that $PGF_{2\alpha}$ represents a key substance eliciting uterine hypercontractility and dys orrheic pain It also appears that the uterus dysmenorrheic subjects has a similar sensitivity to $PGF_{2\alpha}$ and PGE_2 as in normal women If this conclusion is correct and valid as well during menstruation it would mean that dysmenorrheic pain should rather result from an increased intra uterine formation of $PGF_{2\alpha}$ than be the expression of an increased uterine sensitivity to the compound

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THE BEHAVIOUR OF MICROSOMAL MONO ELECTRON CARRIERS IN ADULT AND FETAL LIVER AND IN PLACENTA THROUGHOUT PREGNANCY

P Paparella F Castaldo T Terranova R Romor and A Bompiani

From the Institute of Obstetrics and Gynecology (Head Prof A Bompiani) and the Institute of General Pathology (Head Prof T Terranova) Catholic University Rome Italy

act The activities and contents of microsomal -electron carriers (NADPH cytochrome *c* reductase H-cytochrome b_5 reductase cytochrome P-450 and hrome b_5) in the liver of 160 pregnant rabbits and response to phenobarbital (PB) administration were l to be different to that of non pregnant animals and ry depending on the period of gestation In fetal liver n placenta the activities and contents of mixed func oxidase system enzymes are very low and increase the mid gestation up to the term of pregnancy PB ither no effect or decreases the enzyme levels The tions of enzyme content and activity in maternal liver the different response to PB are related to the onal modifications of pregnancy The behaviour of -electron carriers in fetal liver can be related to the ss of maturation of this organ The effect of PB can ue to the interference of the drug with steroid bolism The behaviour of mixed function oxidase m enzymes in placenta can be related to the proces f maturation and ageing of the organ

well known that the mixed function oxidase m is of great importance in the metabolism of s of hormones etc (16 53) Microsomal mixed tion oxidase system enzymes are present in low quantities in embryonic tissues (fetal liver) in placenta After birth they increase progres y until they reach adult levels in a specific th of time depending on the animal species con red (7 8 10 11 17 20 21 27 35 37 40 44 47 ›1 56 57 60 66)

he aim of this work is the following (*a*) to study quantitative relations and the behaviour of the osomal mono-electron carriers (of cytochrome 0 of cytochrome b_5 of NADPH cytochrome *c* ictase and of NADH cytochrome b_5 reductase) naternal and in fetal liver and in placenta of nt (*b*) to study the microsomal mono-electron carriers after administration of an enzymatic in ducer (18) phenobarbital (PB) The results obtained by others on this subject do not all agree (1 3 12 36 52 54 55 62–64)

Our results show that (*a*) in rabbit s liver gesta tion modifies the levels of mixed function oxidase system enzymes variations are different in each one of the four enzymes response to administration of PB is different to that of the non pregnant animal and varies depending on the period of gestation (*b*) in fetal liver and in placenta the mixed function oxidase system enzymes are very low at mid gestation and increase at term PB treatment is inef fective or acts as an inhibiting factor on the mixed function oxidase system enzymes

The mechanism responsible for these modifica tions are discussed

MATERIALS AND METHODS

17 white New Zealand female rabbits weighing 2 5–3 5 kg and 160 pregnant rabbits weighing 2 5–4 kg were used A treatment was effected with a subcutaneous injection of 30 mg of sodium phenobarbital (PB) per kg/body weight each day for three days before the animals were killed This was done by means of a blow on the head followed by cervical dislocation always at the same time of the day (9 a m) Microsomal drug metabolizing enzymes were de termined on pooled tissue from all the animals On the 12th day of gestation determinations on fetal liver were not carried out as material was insufficient Livers and placentae which were rapidly removed after death were poured into 0 15 M KCl containing 50 mM Tris HCl buf fer pH 7 5 at 0–4 C

The microsomal fraction obtained according to Omura and Sato (39) was suspended in the above mentioned medium yielding a protein concentration of about 15 mg/ml For fetal liver and placentae in the earlier stages of gestation since there was very little tissue it was not

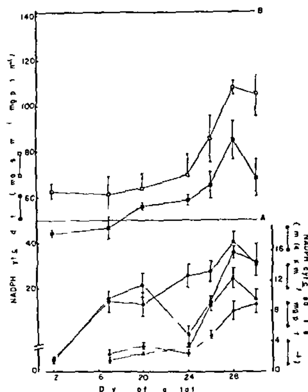


Fig 1 Kinetics of microsomal NADPH cytochrome *c* reductase from various organs in rabbits at different pregnancy ages ■—■ maternal liver ▲—▲ fetal liver ●—● placenta □—□ maternal liver △—△ fetal liver ○—○ placenta after 3 days treatment with PB (30 mg/kg b wt s c) Line A represents the level of microsomal NADH cytochrome c reductase from liver of non pregnant control animals line B from non pregnant PB ated animals The enzyme activity has been measured escribed in Materials and Methods

*possible to obtain the same concentrations hence con*centrations close to 15 mg/ml were used Protein were determined by the biuret method (32) NADPH cytochrome *c* reductase was measured following cytochrome *c* reduction at 546 nm in the presence of NADPH (65) NADH cytochrome b_5 reductase was measured following NADH oxidation at 340 nm in the presence of potassium ferricyanide as electron acceptor (59) Cytochrome P-450 and cytochrome b_5 were determined by a dual wavelength split beam Aminco Chance spectrophotometer The amount of cytochrome b_5 was calculated on NADH reduced samples using $\Delta\varepsilon(424\text{–}409\ nm) = 165\ cm^{-1} \times mM^{-1}$ (14) Cytochrome P-450 was measured on CO treated—dithionite reduced—microsomes using $\Delta\varepsilon\ (450\text{–}490\ nm) = 91\ cm^{-1} \times mM^{-1}$ (29)

RESULTS

NADPH cytochrome c reductase

In *maternal liver* the enzymatic activity of NADPH cytochrome *c* reductase increases progressively from the 17th to the 28th day of gestation and increases slightly after PB treatment On the 30th NADPH cytochrome c reductase is reduced the PB induction maintained (Fig 1)

Enzymatic activity in *fetal liver* is very low the 24th day of gestation and is not modified by After the 24th day it increases progressively slightly inhibited by PB On the 30th day have decreased and are not modified by the treatment (Fig 1)

In *placenta* activity of NADPH-cytochrome reductase is very low on the 12th day Afterwards increases and reaches its maximum value on 28th day Initially the PB treatment is ineffective and is inhibiting in the second stage of gestation (Fig 1)

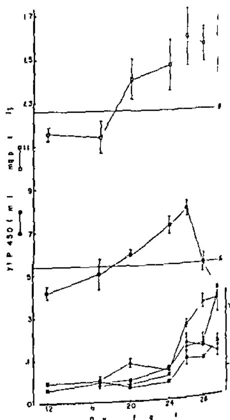
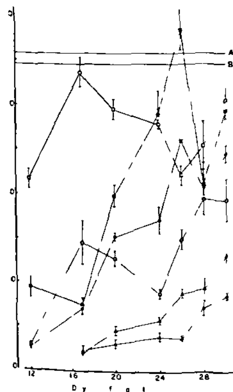


Fig 2 Kinetics of microsomal cytochrome P-450 in various organs in rabbits at different pregnancy ■—■ maternal liver ▲—▲ fetal liver ●—● placenta □—□ maternal liver △—△ fetal liver ○—○ placenta after 3 days treatment with PB (30 mg/kg b wt s c) A represents the level of microsomal cytochrome from liver of non pregnant control animals line B non pregnant PB treated animals The enzyme has been measured as described in Materials and Methods

-hrome P-450

-ontent of cytochrome P-450 in *maternal liver* the 17th day of gestation increases progres y up to the 26th day Afterwards it decreases to itial values PB treatment on the 26th day of tion increases the content of cytochrome P-450 , 100% and by about three times as on the 30th day when basic values are very Fig 2)

e content of cytochrome P-450 in *fetal liver* is low up to the 24th day and increases rapidly in ist days of gestation PB determines a marked ase of enzyme content on the 26th and the day of gestation it is ineffective on the 30th Fig 2) The content of cytochrome in *placenta* fetal liver is very low up to the 24th day of



3 Kinetics of microsomal NADH-cytochrome *b* re ise from various organs in rabbits at different preg y ages ■—■ maternal liver ▲—▲ fetal liver ● placenta. □—□ maternal liver △—△ fetal liver O placenta after 3 days treatment with PB (30 mg/kg t s c) Line A represents the level of microsomal DH-cytochrome b_5 reductase from liver of non preg control animals line B from non pregnant PB ed animals The enzyme activity has been measured scribed in Materials and Methods

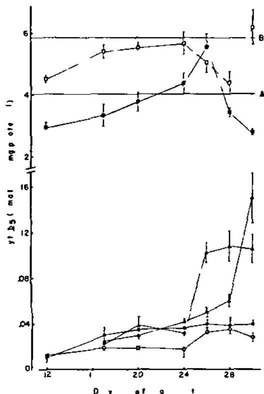


Fig 4 Kinetics of microsomal cytochrome b_5 from various organs in rabbits at different pregnancy ages ■—■ maternal liver ▲—▲ fetal liver ●—● placenta □—□ maternal liver △—△ fetal liver O—O placenta after 3 days treatment with PB (30 mg/kg b wt s c) Line A represents the level of microsomal cytochrome b_5 from liver of non pregnant control animals line B from non pregnant PB treated animals The enzyme activity has been measured as described in Materials and Methods

gestation Later cytochrome P-450 increases PB treatment determines slight inhibitions from the *24th to the 28th day (Fig 2)*

NADH cytochrome b_5 reductase

NADH-cytochrome b_5 reductase activity in *maternal liver* is by far inferior to that of the controls up to the 17th day of gestation It has a high and rapid increase up to the 26th day and decreases in the following days PB treatment which is ineffective in non pregnant animals causes an increase of NADH cytochrome b_5 reductase between the 12th and the 20th day in the days that follow it is either ineffective or has an inhibiting effect on the activity of the enzyme (Fig 3)

In *fetal liver* NADH-cytochrome b_5 reductase increases progressively starting from the 17th day

The enzyme activity is inhibited by PB treatment (Fig 3)

In *placenta* the enzyme's behaviour corresponds to the one observed in maternal liver The effects of PB treatment are variable depending on the period of gestation (Fig 3)

Cytochrome b_5

Cytochrome b_5 in *maternal liver* is initially present in concentrations lower than those of the controls and increases up to the 26th day It goes back to the initial values after the 26th day PB treatment determines a variable increase of the cytochrome b_5 concentrations depending on the day considered (with the exception of the 26th day when this treatment is ineffective) (Fig 4)

In *fetal liver* the content of the enzyme is very low up to the 24th day it increases considerably and rapidly from the 24th to the 26th day PB increases the concentration of the enzyme on the 30th day During the other days it is either ineffective or decreases the content of the enzyme (Fig 4)

In *placenta* there is a slight increase during the first few days (12th and 17th) after which these values remain constant After PB treatment the content of the enzyme decreases (Fig 4)

DISCUSSION

Maternal liver Numerous observations show that in the course of gestation there are modifications of metabolism of drugs (6 13 19 28 48) of the mixed function oxidase system enzymes content (19 36 55) and of the response to treatment with inducers (36 55) Furthermore it has been observed that in male rats the metabolism of drugs *in vivo* decreases after estradiol treatment (50) and that oral treatment with combinations of estrogen and progestin slows down the metabolism of antipyrine (38) These observations suggest that the effects of pregnancy on the metabolism of drugs may depend on hormonal variations Our results show that during pregnancy the levels of microsomal mono-electron carriers in maternal livers are generally decreased Variations are in relation to the stage of gestation PB in a pregnant animal does not produce the same effects as in a non pregnant animal During pregnancy PB scarcely induces the NADPH cytochrome *c* reductase it clearly induces—and sometimes even to a higher degree than that of controls—cytochrome P-450 it considerably induces NADH cytochrome b_5 reductase [illegible] does not modify this enzyme in controls [illegible] fects on cytochrome b_5 are different accord[illegible] the period of gestation The scarce indu[illegible] NADPH cytochrome *c* reductase—rate limi[illegible] zyme of drugs oxidation (9 15 31)—by PB therefore explain the reduced metabolism of [illegible] drugs during gestation The slight induct[illegible] NADPH cytochrome *c* reductase by PB has [illegible] been observed in female non pregnant rabbi[illegible] in male rabbits treated with HCG (4? 43) [illegible] clusion we can assume from previous obser[illegible] (41) and from this work that the variations [illegible] mixed function oxidase system enzyme levels [illegible] the different response of maternal liver to trea[illegible] with PB may depend on hormonal modifica[illegible]

Fetal liver Observations on the levels a[illegible] tures of drug metabolizing enzymes in fetal li[illegible] numerous and results do not always agree ([illegible] 33 46 52 62) Our observations demonstra[illegible] the levels of drug metabolizing enzymes [illegible] gestation are very low and increase prog[illegible] during gestation Some authors have noted [illegible] blood progesterone levels decrease starti[illegible] mid pregnancy (4 22 34) and that the horm[illegible] an inhibiting effect on the mixed function [illegible] system enzymes (5 23–?6 58 61) These ob[illegible] tions could indicate that progesterone can be [illegible] sponsible for the behaviour of drug metab[illegible] enzymes during pregnancy As far as the eff[illegible] PB are concerned it has been noted that P[illegible] generally an inhibiting effect on enzyme [illegible] which varies according to the stage of ge[illegible] Since PB interferes with the metabolism of s[illegible] (30) it is probable that the inhibiting effects [illegible] may be attributed to hormonal variations [illegible] therefore be concluded as probable that th[illegible] ent levels of the drug metabolizing enzymes [illegible] liver and their variations in the course of pre[illegible] may be related as in the case of maternal l[illegible] hormonal variations taking into due conside[illegible] however the problems pertaining to the m[illegible] of the organ

Placenta It has been demonstrated th[illegible] capacity of placenta to metabolize drugs [illegible] cording to the stage of gestation (? 10 12 [illegible] 46) and that for some drugs it decreases [illegible] progress of pregnancy (2 10 33) The result[illegible] experiments show that the mixed function ox[illegible] system enzymes are originally at very low le[illegible] From the 12th day the NADPH cytochrom[illegible]

se and NADH cytochrome b_5 reductase pro- vely increase towards the term of gestation tiafter having reached the highest point of con ation begin to diminish This decrease be more intense if pregnancy is prolonged nd term (45) Similar behaviour has been noted man placenta in the course of pregnancy at and beyond term (44) Cytochrome P-450 and hrome b_5 are at very low levels until the 24th then they slowly increase towards term This viour of mixed function oxidase system en s does not allow us to draw definite conclu However the behaviour observed i e very nitial values the increase that follows and the ase at term is probably related to the stage of ration and age of the placenta

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EVALUATION OF FETAL MATURITY BY AMNIOTIC FLUID CREATININE CONCENTRATIONS AND LECITHIN/SPHINGOMYELIN RATIO

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act In a material of 144 samples of amniotic fluid the last trimester creatinine concentration leci sphingomyelin (L/S) ratio and their correlation have examined Amniotic fluid creatinine concentration) increased gradually through the last trimester up weeks (273–279 days p m) with median values of 2 00 ml at 37 weeks and 2 5 mg/100 ml at 39 weeks tion The great range makes a f c of doubtful value sessment of gestional age in individual samples The lation between a f c and L/S ratio was highly ficant (Kendall s T=0 56) Even so lung maturity ot be predicted from a f c A low L/S ratio with ≥2 mg/100 ml was found in 8–9% while a f c 9 mg/100 ml was combined with L/S ratios ≥? in a number of cases A f c <1 1 mg/100 ml was invari correlated with low L/S ratios

purpose of the present study has been to uate a f c in assessment of gestational age and xamine the correlation between a f c and the ratio A f c estimation is available in most ratories but many hospitals have no access to spholipid analysis A great number of studies e shown the relation between L/S ratio and the iratory function in the newborn Instead of L/S in evaluation of lung maturity a f c could be d if a good correlation existed among these two ameters

MATERIAL AND METHODS

notic fluid creatinine and L/S ratio have been ex ned in 144 samples of amniotic fluid from 97 pregnant nen with known gestational age delivered at the De ment of Obstetrics and Gynaecology Rikshospitalet n September 1974 – December 1975 132 of the samples e taken in the last trimester and 12 samples between 26–28 weeks of gestation Amniotic fluid was collected by transabdominal amniocentesis or at caesarean section In 14 cases a transvaginal puncture was performed during spontaneous delivery Samples contaminated by blood or meconium were discarded The number of patients and samples in the different groups of patients are presented in Table I Among the patients with normal pregnancies 13 were delivered by caesarean section because of mechani cal disproportion

The a f c was analyzed by Autotechnicon SM 12/60 method (modified Jaffe s reaction with alkaline picrate) and L/S ratio determinations were performed by a mod ified Gluck s method as previously published (15)

The results of a f c and L/S ratio determinations were correlated to gestational age and to each other and the correlation between the two parameters was statistically evaluated

In samples taken within one week prior to delivery the results were related to the clinical outcome with regard to respiratory function and the a.f c was compared with the weight of the fetus A growth retarded child is defined as a child ≤2 5 percentile according to Bjerkedal et al (2) The assessment of the respiratory distress syndrome (RDS) has been previously published (9) Typical symptoms last ing for less than 24 hours are referred to as transitory RDS

Table I *Groups of patients included in the material*

Groups of pats	No of pats	No of samples
Rhesus immunized	38	80
Diabetes mellitus (White C D F)	?4	26
Preeclampsia and/or growth retardation	8	11
Normal pregnancies	27	27
Total	97	144

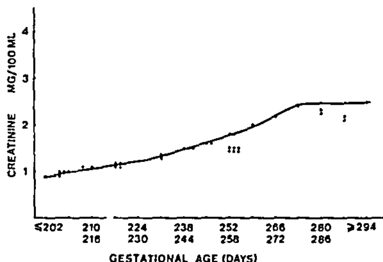


Fig 1 Creatinine concentration[s] ... samples of amniotic fluid ... tional age ● One ... — median values

RESULTS

The a f c increased gradually through the last trimester up to 39 weeks (273–279 days p m) As seen in Fig 1 the increase in the median values was nearly linear with levels of 2 mg/100 ml at 37 weeks gestation and 2 5 mg/100 ml at 39 weeks Prior to 35 weeks gestation values of ≥2 mg/100 ml seem to be exceptional and occurred in our series only in one patient with preeclampsia and a growth retarded fetus After 35 weeks there is a great range in the results obtained and a f c <2 mg/100 ml occurred occasionally even after 40 weeks

The different categories of patients are not valid for comparison due to different numbers and differ gestational age However the a f c from the ...tic mothers seem to be distributed as for ... immunized while the few preeclamptic patients (8 pats) have values in the upper part of the range Maternal serum creatinine was ≤0 9 mg in 4 of these patients and was not examined in the remaining 4 mothers with mild preeclampsia was not of a degree likely to have any ef... renal function There is no correlation ... a f c and the weight of the fetus (Fig 2)

The L/S ratios demonstrate the normal ... cording to gestational age (Fig 3) and the ... values reach the considered critical value of ... about 35 weeks However there are great ... ual variations With a gestational age of ≥ ... the L/S ratio was 1 9 in one sample and ... remaining 27 On the other hand a L/S ratio ... was not found in the 49 specimens taken prior ... 34 weeks No special trend was found for L... ratios among the different categories of pa...

There is a positive correlation between a f c ... L/S ratio The numeric variation in L/S ra... much greater than in a f c and in Fig 4 the co... tion is illustrated on a semilogarithmic sc... Kendall s correlation coefficient between a f c ... L/S ratio was calculated to 0 56 which is h...

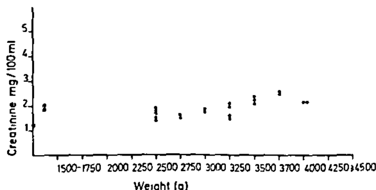


Fig 2 Creatinine concentrations ... samples of amniotic fluid obtained ... one week of delivery related to the ... of the newborn ● One sample from a ... with no growth retardation ○ one ... from a growth retarded child ... percentile—see text)

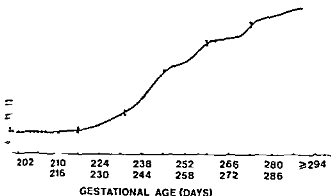


Fig 3 L/S ratio in 144 samples of amniotic fluid related to gestational age ● One sample of amniotic fluid — median values

icant ($P<0.0005$) A f c levels ≥2 mg/100 ml only associated with L/S ratios below 2 in 6 ...les only 4 of these really low (<1 8) L/S ...s ≥2 were however associated with a f c ...s in the range 1 1–1 9 in 27 samples A f c ... mg/100 ml were invariably associated with low ratios

... 40 cases the samples were obtained at delivery ... in a further 20 within one week prior to deliv... Six of the 60 children developed RDS Two ...dren from diabetic mothers who were only ...ly affected by RDS had L/S ratio 2 1 and 2 6 ... with a f c >2 mg/100 ml The remaining 4 had ... ratios of 0 6 0 8 1 1 and 1 2 with correspond... a f c values 1 1 1 8 1 6 and 1 5 (Fig 5) No ... died from RDS

DISCUSSION

... consistant rise in a f c during pregnancy is ... documented by many authors (1 3 5 7 8 12 13 14 16) Values of ≥2 mg/100 ml are ...kely to be obtained prior to 35 weeks and indi... that the gestational age is probably 37 weeks or ...e but the great range makes a f c determina...s of limited value in individual samples a ...ement made in several papers (6 11) Values <2 .../100 ml occurred even at a gestational age of 40 ...ks

...oopnarinesingh (14) and Weiss et al (16) found ...itive correlation between birthweight and ...c —the latter up to a fetal weight of 2 500 g In ... study we found no correlation with the fetal ...ight Only 9 of the 60 children referred to were delivered prior to the 36 weeks Premature infants generally have lower birthweights and a f c values but beyond that there is obviously no correlation between a f c and the weight of the fetus This gives support to the theory that a f c reflects the maturation of renal function in the fetus rather than its muscle mass and purine metabolism The high a f c values in patients with preeclampsia associated with growth retarded fetuses is noteworthy and may be a result of reduced placental exchange and/or oligohydramnios Cassady et al (3) Roopnarinesingh (14) Bertram et al (1) and Løfstrand et al (10) have also stated that a f c is ele...

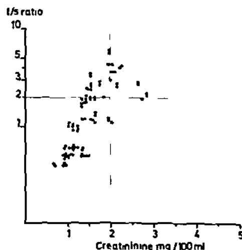


Fig 4 The correlation between L/S ratio and the creatinine concentrations in 144 samples of amniotic fluid illustrated on a semilogarithmic scale ● One sample of amniotic fluid

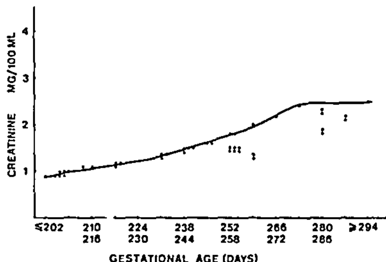


Fig 1 Creatinine concentrations in samples of amniotic fluid related to gestational age ● One sample of amniotic fluid — median values

RESULTS

The a f c increased gradually through the last trimester up to 39 weeks (273-279 days p m) As seen in Fig 1 the increase in the median values was nearly linear with levels of 2 mg/100 ml at 37 weeks gestation and 2 5 mg/100 ml at 39 weeks Prior to 35 weeks gestation values of ≥2 mg/100 ml seem to be exceptional and occurred in our series only in one patient with preeclampsia and a growth retarded fetus After 35 weeks there is a great range in the results obtained and a f c <2 mg/100 ml occurred occasionally even after 40 weeks

The different categories of patients are not valid for comparison due to different numbers and different gestational age However the a f c from the diabetic mothers seem to be distributed as for rhesus immunized while the few preeclamptic patients (8 pats) have values in the upper part of the range Maternal serum creatinine was ≤0 9 mg in 4 of these patients and was not examined in the remaining 4 mothers with mild preeclampsia was not of a degree likely to have any eff renal function There is no correlation be a f c and the weight of the fetus (Fig 2)

The L/S ratios demonstrate the normal re cording to gestational age (Fig 3) and the values reach the considered critical value of about 35 weeks However there are great ind ual variations With a gestational age of the L/S ratio was 1 9 in one sample and ≥ remaining 27 On the other hand a L/S ra was not found in the 49 specimens taken pr 34 weeks No special trend was found for ratios among the different categories of pa

There is a positive correlation between a L/S ratio The numeric variation in L/S ra much greater than in a f c and in Fig 4 the cor tion is illustrated on a semilogarithmic sc Kendall s correlation coefficient between a f c L/S ratio was calculated to 0 56 which is h

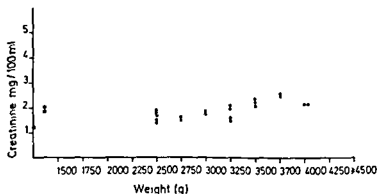


Fig 2 Creatinine concentrations in samples of amniotic fluid obtained within one week of delivery related to the weight of the newborn ● One sample from a child with no growth retardation O one sample from a growth retarded child (below percentile—see text)

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PRESENCE OF ANTI-c IN THE SERUM OF 42 WOMEN GIVING BIRTH TO c POSITIVE BABIES SEROLOGICAL AND CLINICAL FINDINGS[1]

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act During routine ante natal testing during the 1953–73 anti-c was found in the serum of 63 wom wenty four of them had received blood transfusion usly and of these 22 were multigravidae In 39 wom egnancies alone were responsible for the immuni . The anti-c titres of the 42 women giving birth to c ve babies showed that the probability of developing olytic disease increases with higher titres But low by no means exclude the existence of such disease ng the 4? c positive babies 32 had a positive direct lobulin test Some of the affected infants had a seri legree of haemolytic disease

eporting to the clinicians the finding of anti-c in of pregnant women we sometimes feel that the mation is not taken as seriously as desirable ever looking through the literature we found ively few data on the clinical importance of this body in pregnancy Most of the available infor ion comes from reports on a limited number of s of haemolytic disease of the newborn (1 2 4 A greater number of cases was described by ner et al (7) However such cases are some s selected They will therefore not give a true ure of the clinical importance of anti-c in preg cy how often the antibodies lead to haemolytic ase of the newborn (HDN) the degrees of se ity of the disease and the prognosis in the af ted infants

Ve therefore analysed our cases of anti-c found routine antenatal testing during the period 1953–73 We here tried to find out whether the anti body formation had been stimulated by previous blood transfusion or pregnancies and looked for a correlation between the maternal antibody titre and the occurrence of HDN In the affected babies we attempted to estimate the degree of the disease on the basis of the available serological and clinical information

MATERIALS AND METHODS

In our routine antenatal serological testing all blood sam ples are tested not only for anti D but for other irregular blood group antibodies as well Thus all sera are ex amined with saline albumin indirect antiglobulin and en zyme methods against the Rh antigen c We collected from our laboratory records for the period 1953–73 the cases of anti-c diagnosed during pregnancy

When Rh antibodies of any specificity are demon strated a blood sample is obtained from the husband for determination of the probable Rh genotype All cases where the husband was c negative and the antibody could not have any bearing upon the pregnancy were excluded from the present study So also were cases where addi tional blood group immune antibodies were demonstrable since it would be difficult to assess the relative importance of the different antibodies

Our series consists of 63 women representing 69 preg nancies with anti-c Two pregnancies ended in early abortion The deliveries took place at a number of hospi tals We obtained information on the babies in 61 of the 67 cases The clinical data received were heterogeneous and in some cases rather inadequate Forty two c positive babies in whom the results of the direct antiglobulin test are known will be described in this paper

Four infants known to be c negative and 14 with an unknown Rh genotype were excluded So also positive baby in whom the result of the direct

[1] preliminary report of the study was presented at the Congress of the International Society of Blood Trans on Helsinki 1975

Table I *Previous blood transfusions in 63 pregnant women with anti c*

Antibody detected in pregnancy	Transfused women	Non transfused women	Total
No 1	2	0	2
No 2	6	8	14
No 3	4	9	13
No ≥4	12	22	34
Total	24	39	63

test was not available this baby gave no evidence of haemolytic disease Among the 14 infants with unknown Rh genotype eight had a negative direct antiglobulin test In the remaining six the outcome of the test is unknown However one of these babies reportedly had HDN

When antibody titres are given in the sequel it unless otherwise stated always refers to the results of the indirect antiglobulin test performed on *cde/cde* cells

RESULTS

Among the 63 pregnant women with anti-c 24 had a history of previous transfusions (Table I) Only 2 of the 63 cases were diagnosed during the first pregnancy Both women had been transfused In 47 women antibodies were first observed in the third or a later pregnancy Only one third of these women had been transfused while the remainder were immunized as a result of pregnancy and delivery ne

Of the 42 babies known to be c positive 32 had a positive direct antiglobulin test and HDN In the last ante natal examination one day to 4 weeks before delivery the women with c positive babies had antibody titres up to 1024 in the indirect antiglobulin test (Table II)

The ten mothers with healthy infants all had titres of 8 or below In two of them the antibody was demonstrable with enzyme treated cells only while the antibody in one case reacted with albumin and papain methods but not by the indirect antiglobulin technique

Among the mothers of babies with haemolytic disease two had particularly high titres 512 and 1024 In the 30 others the titres ranged from 1 to 128 with a titre of 8 or lower in 14 mothers (Table II)

We received information about the haemoglobin values on the first day of life in 21 of the 3[illegible] with haemolytic disease (Table III) In the ta[illegible] infants are grouped according to whether e[illegible] transfusions were given or not The h[illegible] concentrations refer to cord blood except [illegible] cases where the kind of blood examined [illegible] stated Only one baby had a grave anaemia [illegible] six had intermediate haemoglobin values

The 9 *transfused* babies were all born a[illegible] The mother of the gravely anaemic infant ha[illegible] anti-c titre of 512 This baby to whom [illegible] return in the discussion had in the cord b[illegible] haemoglobin concentration of 7 6 g and a b[illegible] concentration of 11 4 mg per 100 ml It rec[illegible] exchange transfusions but developed cerebr[illegible] orders probably caused by bilirubin damage [illegible] two transfused infants with intermed[illegible] haemoglobin values recovered uneventfully [illegible] maternal antibody titres were 4 and 64 re[illegible]tively

The 4 of the 9 transfused babies with a [illegible] cord blood haemoglobin all developed patholo[illegible] bilirubin values Three of them recovered un[illegible]fully The fourth receiving two exchange tr[illegible]sions developed a pathological electroence[illegible]gram This was presumably caused by a temp[illegible] respiratory and cardiac arrest during the first [illegible]fusion The antibody titre in the mother was [illegible]

Of the two transfused babies on whom we [illegible] no information about the haemoglobin values [illegible] died after exchange transfusion with in comp[illegible] blood of the Rh type *cde/cde* The other rec[illegible] without complications

Among the 23 *non transfused* infants one [illegible] initially had a normal haemoglobin concentr[illegible] died Autopsy revealed kernicterus a pa[illegible] men ovale and atelectasis of the lungs The [illegible] body titre of the mother was 8 The remain[illegible] babies recovered without sequelae

Table II *Occurrence of haemolytic disease re[illegible]lated to anti-c titres in the mothers*

	Titres by the indirect antiglobulin test			
	≤8	16–128	512 1024	[illegible]
HDN	14	16	[illegible]	[illegible]
No HDN	10	0	0	[illegible]

III *Exchange transfusions correlated to -globin concentration (g per 100 ml) on the -y of life*

	<10	13–15	≥17	Un known	Total
ised s	1	2	4	2	9
ansfused s	0	4	10	9	23
	1	6	14	11	32

DISCUSSION

present series of pregnant women with anti-c nsitization was in more than 60% of the cases d by pregnancies and deliveries alone As then be expected the proportion of multiparous n is quite high In two cases only the anti formation was almost certainly the result of ous transfusions alone The antibody was nt in the first blood sample drawn in the 3rd th month of pregnancy respectively In about of the cases the immunizing stimulus may have previous blood transfusion previous preg y or perhaps most likely both Our findings n agreement with those of Spielmann & Seidl in their cases of HDN caused by anti-c the inization could not in any case be claimed to be esult of previous transfusion alone The anti formation was either a result of previous nancies or of a combination of previous nancies and transfusions

s already pointed out (Table II) the anti-c titres low in the mothers giving birth to infants not by HDN Concerning the 32 babies with N the antibody titres were in 18 mothers 16 or er in 14 mothers 8 or lower The great propor of low titred antibodies in this group is notable ome cases the titres might have been higher if mined at term However in 6 of these 14 cases last titration was performed within one week ore delivery and in 2 cases only the interval was ong as 4 weeks It may thus be concluded that le the probability that the babies will be affected reases with higher titres low titres by no means lude the existence of haemolytic disease

As previously mentioned we tried to exclude m the present series women who in addition to i-c also had other blood group immune anti dies In this connection the possible presence of anti E of course represents a special problem as CCDEe (R R_1) cells were not always available However 22 of the babies with a positive direct antiglobulin test are known to be E negative Six infants are CcDEe (R_1R_2) and 3 have an *Ee* father but have not been E grouped themselves Among these 9 babies only one needed exchange transfu sion a possible simultaneous presence of anti E cannot have contributed much to the severity of the disease in these infants

In a single case anti E is known to be present in addition to anti-c This is the case of the gravely anaemic infant already mentioned Four weeks be fore delivery the anti-c titre (against *cde/cde* cells) was 0 in saline 128 in albumin 512 by the indirect antiglobulin test and 256 against papainized cells In the same sample the anti E titre (against *CDE/CDe* cells) was 64 in saline 64 in albumin 32 by the indirect antiglobulin technique and 128 against papain treated cells The baby was at the hospital found to be C+ c+ D+ E− However at our laboratory the father s cells gave clear-cut nega tive reactions with several anti-e sera suggesting an erroneous E typing of the infant Anyhow the anti E of the mother seems to be predominantly IgM and the incomplete anti-c must be assumed to have the major responsibility for the grave haemolytic disease

In the large series presented by Giblett (3) anti-c caused over 3% of the cases of HDN With the marked decline in the total number of cases of HDN resulting from the current Rh(D) prophylaxis the proportion of HDN cases due to anti-c will in crease Although anti-c erythroblastosis most often is mild to moderate severe cases with intrauterine anaemia may occur Therefore amniocentesis may *be indicated to select cases where labour should be* induced or intrauterine transfusion given

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NEONATAL AND PROSPECTIVE FOLLOW UP STUDY OF INFANTS DELIVERED BY VACUUM EXTRACTION (VE)

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act Forty infants delivered by vacuum extraction been studied in the neonatal period—neurological ination neonatal CSF-examinations skull X ray ex ation transillumination and sonoencephalography l at 14 months of age—developmental and be ural evaluation neurological examination skull examination sonoencephalography and electro- phalography Two infants died in the neonatal period n both cases a life threatening situation for the fetus red immediate delivery CSF cytological signs of orrhage were observed in 42% of the 26 infants who a successful lumbar tap compared to 10% found in al deliveries The result of the neonatal neurological did not differ from that in a control group The result skull X ray examination and sonoencephalography also within normal limits In the follow up study vioural problems were found in 25% but otherwise few abnormalities were found The deviations found ot for the present indicate any later signs of brain ns It is concluded that this prospective study has n that VE-delivery in fullterm babies seem to imply isk of serious cerebral sequelae Further follow up es at a later age in order to evaluate the incidence of lled minimal brain damage in VE-delivered children required

e the introduction of the vacuum extraction) delivery method in Sweden by Malmstrom in 4 (9) the number of infants delivered by VE have numbered forceps deliveries (Table I) Earlier orted studies with regard to the outcome of -delivered infants have mostly been retrospec i e taking into account perinatal events sev l years after the delivery (for review see (3)) spective studies with thorough perinatal obser ions and examinations followed by repeated ex inations during the first year of life are few nsequently we have performed the present in tigation in order to evaluate perinatal (obstetrical and neonatal) events at VE-deliveries prospectively in relation to later development and long term sequelae

MATERIAL

The material comprises a consecutive series of 48 instrumental deliveries (VE and/or forceps) out of 1 169 live births during a 4-month period 1971–1972 In 4 cases forceps were applied In 4 deliveries forceps were used because the vacuum extractor became detached The present report deals with the 40 infants delivered by VE only

The mothers were between 19 and 40 years of age (mean age 27 years) Thirty-one mothers were primi-gravidae The gestational age at birth was between 38 and 41 weeks in 27 infants more than 41 weeks in 9 infants and 37 weeks or less in 4 infants There were 22 girls and 18 boys Five infants were large for gestational age and one infant small for gestational age

The material was divided into 2 groups according to the indication for VE-delivery (Table II) *Fetal indication* i e irregular fetal heart rate ($n=18$) *Maternal indication* i e standstill in labour or some other obstetrical factors as shown in Table II ($n=22$)

The number of low and mid VE did not differ between the two groups High VE was never used during this study The control group for the neonatal neurological study included 28 full term neonates with a normal pre and perinatal period and non-instrumental delivery

Parental and institutional consent had been obtained for the examinations performed in the postnatal period in every infant included in this study χ^2 test was used for group comparisons

Part I Neonatal study

METHODS

Neurological examination In the schedule for the neonatal neurological examination 21 items were used

Table I *Incidence of forceps and vacuum extraction (VE) deliveries in the Obstetrical Department of the University Hospital Lund*

	Period		
	1950–1954	1960–1964	197?
Forceps	2 5 %	0 7 %	0 6 %
VE	–	2 6 %	3 9 %
Total number of deliveries	11 801	13 766	3 578

Palmar grasp
Plantar grasp
Babinski s sign
Withdrawal reflex
Rooting response
Sucking response
Facial movements
Traction test
Head control in sitting posture
Head movement in prone position
Crawling in prone position
Stepping movements
Moro response
 threshold
 abduction–extension
 abduction–flexion
Rotation test
Doll s eye test
Muscle tone
 or activity
 type
 amount
Sensitivity to touch and stimulation

The examination was performed on the third day of life 2 hours after a meal and in adequate state according to Prechtl & Beintema (11) Optimal result for each item was scored one The scores were added up to a total score and thus the maximum obtainable value will be 21 According to the total score the material was divided into quartiles

At the neurological examination the skull was examined for external traumatic scalp deformity and excoriation of the skin Measurements of head circumference and transillumination of the skull were also made

Cerebrospinal fluid (CSF) examination Cytological CSF examination was performed on the third day of life according to the method of Sum... This method involves a one hour ... the CSF sample in a glass cylinder fixed by ... on a microscopic slide and thereafter the supernatant fluid is gently sucked away the cylinder removed the preparation air-dried and stained finally examined in a light microscope Presence of erythrophages and siderophages is considered indicative of cerebral or spinal haemorrhage

The content of *lactate and pyruvate* in CSF measured enzymatically (15) The lactate/pyruvate ratio is indicative of the cerebral energ... thus a tool for measuring cerebral oxygen deple...

Sonoencephalography was performed on the third day of life The mid-echo position ... and the lateral ventricular index calcul... ing to Sjögren (12) *X ray examination of the* ... was performed on the first or second day after ... *The methodology and results are presented* ... follow up study (part II)

RESULTS

Two VE delivered infants died in the neo... period One infant with birthweight 1 550 gram... first of twins was delivered in 31st week of g... tion by VE because of impending twin interloc... The baby cried immediately after birth but became apnoeic and required assisted ventil... The infant died at 18 hours of age and at au... bleeding in the galea cerebellar haemorrhage a tentorial tear and cerebral cellular anoxic d... were found The second infant was a term ... rapidly extracted with a vacuum extractor be... no fetal heart activity could be recorded whe... mother arrived in the labour ward The baby ... resuscitated but died on the second day of life ... periods of fits and apnoea Autopsy showe...

Table II *Indications for VE delivery*

Fetal indication		18
Irregular fetal heart rate	17	
Impending twin interlocking	1	
Maternal indication		22
Secondary uterine inertia	14	
Prolonged second stage	3	
Toxaemia	2	
Epidural anaesthesia	1	
Previous vaginal repair	1	
Retinal ablation	1	
Total number		40

vein bleedings and cerebral ventricular orrhage These two cases are not included in llowing account of the neonatal study results ong the 38 surviving infants 5 had Apgar s at one minute after birth below 7 i e early atal asphyxia was encountered in 13% of the ving VE delivered infants On 4 of these 5 s mid VE was applied—in two infants for a ndication—and on the fifth baby low VE for a ndication

total scores of the neonatal neurological ex ation are presented in Fig 1 No statistically icant differences were found between the elivered infants and those in the control group dividing the VE infants into two groups r quartile and upper three quartiles) according total scores no significant correlation could und either with the indication for VE (maternal al) or the type of VE (mid or low)

e CSF cytological examination showed signs emorrhage (cerebral or spinal) in 11 of 26 s In 12 babies this examination could not be rmed because of parents refusal or was in lete because of unsuccessful lumbar puncture boratory errors In the abnormal CSF samples often only a few erythrophages and sidero es were seen i e the number of pathological was usually not abundant No significant cor ion between the CSF cytological findings and ndication for or type of VE or the neonatal ological examination was found

e CSF lactate and pyruvate analysis was rmed in 31 babies The lactate/pyruvate ratio slightly increased in 2 babies—20 9 and 18 9 ectively—as compared to the upper normal of 17 6 for this age group (15)

noencephalography *performed in 35 infants* ved ventricular index within normal limits i e ±0 03 according to Sjogren (12) and no abnor midline echo deviations

o skull fractures were found

Part II Follow up study

METHODS

4 months of age re-examination was carried out in the iving infants Three infants had left the area leaving a l number of 35 children in the follow up study

entál interview with special attention directed to lems concerning sleeping and feeding habits colics eme sensitivity to sudden sounds developmental milestones and motor aberrations was performed for every VE-delivered infant

A conventional *neurological examination* including evaluation of gross and fine movements speech development as well as head circumference measurement and skull transillumination were performed In addition *EEG* was performed in 34 infants with sleeping records obtained in two-thirds of the infants *Sonoencephalography* was performed in 33 infants as described in the neonatal study (part I)

X ray examination of the skull On the radiograph measurements were made of the greatest length (L) width (W) and height (H) between the internal tables of the skull H is the maximum perpendicular distance between the vault of the skull and the line from the nasion to the posterior margin of the foramen magnum The maximum distance between the inner margins of the mandibular necks was also measured (M) The cranial index (C index) was determined as (H+L+W)/M However due to the normally existing deformity of the skull in the first days after birth only W/M index could be calculated on the neonatal radiographs of the skull The W/M indices from the neonatal and the follow up study could be directly compared whereas the sum of H+L+W and the C index from the follow-up study were compared with known normal values (4)

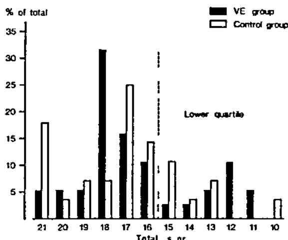


Fig 1 Total scores of the neonatal neurological examination

RESULTS

In the 35 infants studied at 14 months of age the neurological examination showed no abnormalities EEG was slightly abnormal in 2 infants showing unilateral sporadic focal sharp-waves during sleep in one infant and asymmetry of the slower components in the other infant Sonoencephalography and

Table III *Abnormalities in the 14 months of age follow up study (part II) in relation to VE-indication cytological examination and neurological examination in the neonatal study (part I)*

N = number of infants examined at 14 months of age and number of infants VE-delivered on fetal indication abnormal CSF cytology or neonatal neurological examination respectively out of total number of infants exam = CSF sample not obtained

Examination at 14 months of age	*N*	35/38	Fetal VE indication (irregular fetal heart rate) 16/38	Neurological score at 3 days of age within lower quartile 10/38	CSF , of age 11/26
Abnormal EEG	2		2	2	1 (not exam 1)
Increased sound sensitivity	3		2	3	2 (not exam 1)
Behaviour problems	9		2	3	1 (not exam 3)

X ray examination of the skull showed no abnormalities in any infant

In the parental interview the mothers of 9 infants stated single or multiple complaints including disturbed sleeping habits (5 cases) colics (6 cases) breath holding spells (2 cases) and unusual sound sensitivity (3 cases) The last mentioned complaint was confirmed at the examination One of these three infants also had breath holding spells and another had asymmetrical EEG as mentioned above

Correlation to neonatal study (part I) The main abnormalities of the follow up study as related to neonatal observations and examinations are presented in Table III The infants with abnormal EEGs were both delivered by VE for a fetal indication—one with low and the other with mid VE—and belonged to the lower quartile in the neonatal neurological examination One of these babies also had CSF cytological signs of haemorrhage while lumbar puncture was unsuccessful in the other baby

Only 2 of 9 infants with parental complaints of behaviour problems were delivered by VE for a fetal indication and only 3 of these 9 infants belonged to the low quartile in the neonatal neurological examination study Furthermore CSF examination performed in 6 of these 9 infants showed haemorrhage in only one baby

The results of X ray examination of the skull are shown in Table IV Three groups are considered here infants with CSF signs of haemorrhage infants with normal CSF and infants in whom no CSF examination had been performed The calculated indices did not show any difference between the three groups or from normal values Normal X ray examination indices were also found in infants belonging to the lower quartile of the neonatal neurological examination

DISCUSSION

The necessity of taking into consideration the obstetrical situation when evaluating the consequences of VE-delivery must be stressed In the present series two infants died after VE-delivery In both VE was applied because of a threatening intrauterine situation One infant delivered by VE because of impending [illegible] locking several weeks before term. It has [illegible] been stated that VE application in preterm [illegible] should be avoided (10) and in this case [illegible] might have been preferable Thus in the two cases the risk of severe complication was [illegible] able already before the VE application and the method per se might not be the only reason for the unfortunate outcome in these cases

Earlier investigations of cerebral haemorrhage after instrumental deliveries are based on [illegible] findings In these studies the indications for instrumental aid have mostly been fetal [illegible] results are inconclusive (8) In the present investigation CSF cytological signs of [illegible] found in 42% (11 of 26 cases) of the surviving infants and in equal frequency after fetal and [illegible] indications These results should be compared [illegible] the 10% found in normal deliveries (16) and [illegible] found in infants with respiratory distress syndrome (1)

Predictions from the results of the CSF [illegible] must for the present be done cautiously [illegible] cytological findings have been shown to be [illegible]

IV *Skull X ray examination (mean) in relation to CSF cytology*
al values according to (4)

	Neonatal study (age 1–2 d) W/M index	Follow-up study at 14 months of age W/M index	Sum of H+L+W	C index
series	17 2 $n=38$	17 9 $n=28$	453 $n=29$	57 4 $n=29$
signs of haemorrhage	17 5 (16 0–19 0) $n=11$	17 9 (16 8–18 4) $n=8$	450 (430–476) $n=8$	57 9 (54 0–60 1) $n=8$
al CSF logy	17 2 (16 4–17 9) $n=15$	18 1 (16 9–19 2) $n=11$	457 (435–490) $n=12$	58 6 (53 9–60 4) $n=12$
SF mination	16 8 (16 1–17 6) $n=12$	17 5 (16 1–18 7) $n=9$	444 (419–469) $n=9$	56 2 (53 1–59.5) $n=9$
al values	17 3±0 6		441±45	56 0±6 0

mon and of uncertain prognostic value in un plicated concussion in adult patients (14) ever *after perinatal asphyxia we have found* cytological CSF examination has a prognostic e i e normal cytology seems to imply a better nosis as compared with abnormal cytology

In the present investigation there were no cor tions between the CSF cytological finding and other neonatal parameters The results from the nonths examination are also inconclusive with ect to the interpretation of the cytological re s Long term follow up studies over several rs are required to clarify whether any minor bral dysfunction could be related to the abnor CSF cytological findings in the 42% of VE vered infants

he possibility of spinal bleedings as a source for pathological cells in the CSF should also be kept nind when discussing neonatal traumatic nerv system *lesions Towbin (17) has pointed out* t such lesions could easily be overlooked How r there were no neurological signs indicating a injury

The small deviations in the two abnormal EEG ordings as well as the two slightly elevated CSF tate/pyruvate ratios do not permit any conclu- ns Earlier EEG studies have shown disparate ults mainly because of differences in selection of ternal VE indications and age at examination (2 8) CSF lactate/pyruvate studies after VE livery have not been presented before in the liter ure whereas blood lactate and pyruvate analyses ve been found to be normal after VE-delivery (5)

The normal results of the X ray examination of the skull are in agreement with Hickl (8) while Backman et al (2) reported 9 instances of skull *lesions in a series of 101 VE-deliveries However 7* of these cases were high VE

Important questions arise concerning the infants with behaviour problems Is the behaviour of these infants really deviating from normal (and if so be- cause of neonatal lesions?) or are their mothers more anxious and reacting with great alarm to nor mal signals of discomfort in their infants? It should be noted that 7 of 9 infants with behaviour problems had been delivered because of maternal indications (most often secondary uterine inertia) The present study does not allow any definite conclusion al though a possible causative mechanism should be kept in mind Anxiety during delivery may threaten the fetus through maternal hyperventilation causing secondary blood gas changes in mother and placenta resulting in fetal hypoxia (7) More exten *sive studies are needed to clarify the complicated* relationships between mother and infant both be fore and after birth

Taking into account the total strain sustained by the fetus during delivery and the findings at 14 months of age it seems to us that VE-delivery is a rather safe and innocuous method of delivery when applied at full term and according to present obstet rical practice This conclusion is in agreement with earlier reported follow up investigations (2 3 6 18)

The abnormalities observed in the neonatal study and in the follow-up study at 14 months of age warrant further follow-up studies of these children at school age in order to evaluate whether

dence of so-called minimal brain damage (MBD) symptoms is higher in VE-delivered children than in children after non instrumental deliveries

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EFFECTS UPON THE FETUS OF OXYGEN ADMINISTRATION TO THE MOTHER

A Study in Monkey

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…act Catheters were placed into assorted arteries and … of 8 anaesthetized pregnant monkeys and their …es Oxygen sensitive electrodes were also inserted …ntaneously into 3 of the 8 fetuses Periodic samples of …rnal and fetal blood were analyzed for PO_2 PCO_2 and … Oxygen administration to the mothers reliably in…ed the PO_2 of blood taken from the fetal carotid …y and less constantly augmented the PO_2 of blood drawn from the femoral artery and vein During 5–6 …s of study the oxygen tension of fetal blood samples …l animals progressively declined However the most …ted declines in PO_2 values at all fetal sites were regu… observed at those times as—or after—the mothers …rged from anaesthesia At these times also the …nitudes of the increases in fetal blood PO_2 brought …t by administering oxygen to the mothers diminished …kedly and in parallel at all sample sites The closely …lar magnitudes of these various reductions at all fetal …ple sites indicate that the basic mechanisms leading to …eased oxygen delivery lie outside the fetuses and are …t likely due to decreased maternal blood flow to the …us because of increased maternal sympathetic stimula…

These reductions in oxygen delivery to the fetus are …regularly reversed by reanaesthetizing the mothers … studies carried out with oxygen sensitive electrodes …onstrate that administering oxygen to the mothers …ilarly increases oxygen tension of fetal tissues but after … sec delay

…e question whether administering oxygen to …men in labour improves oxygenation of the fetus …s remained unanswered It has been suggested …t 100% oxygen breathing by the mother may …tually reduce rather than increase the oxygen …pply to the fetus because oxygen at high concen…tions may constrict uterine blood vessels (10 18 19) On the other hand numerous studies have shown that administering oxygen to the mother actually improves rather than diminishes the oxygenation of the fetus (4 12 17 20 21 22 25 26)

The present study uses a rhesus monkey model in order to look further into this important question Catheters were placed in blood vessels of mothers and fetuses Blood samples were withdrawn from both and their oxygen tensions compared at different times and under different physiologic conditions Particular attention was paid to defining any differences in oxygen transfer to the fetuses according to depth of anaesthesia of the mothers Oxygen sensitive electrodes inserted into fetal subcutaneous tissues permitted tissue oxygen tension to be followed on a moment by moment basis The time relations between administering oxygen to the mothers and observing changes in oxygen tension of fetal tissues were determined

MATERIAL AND METHODS

Eight pregnant rhesus monkeys near term (154–158 days of gestation) were used Pregnancy length was known with an accuracy of ±2 days Body weight varied between 6.2 and 9 4 kg All animals were anaesthetized with pentobarbital 35 mg/kg I V A warm water mattress was placed beneath the mothers and an overhead heat shield servo-modulated by a rectal thermistor maintained the mothers body temperature within the range 37°–38°C The mothers left femoral artery and vein were exposed and polyethylene catheters were inserted advanced to the level of the midabdomen and fixed in place A hysterotomy was performed and the left leg of the fetus

Table I *pH Determinations during periods of oxygen administration and air breathing in full term monkeys*

MFA=maternal femoral artery MFV=maternal femoral vein FCA=fetal carotid artery FFA=fetal femoral [illegible] FFV=fetal femoral vein

	100% O_2	Air	100% O_2	Air	100% O_2	Air	100% O_2	Air	100% O_2 [illegible]
MFA	7 40	7 41	7 45	7 42	7 45	7 435	7 465	7 49	7 41
MFV	7.35	7.38	7.39	7 40	7 40	7 41	7 43	7 46	7 40
FCA	7.32	7.34	7.36	7.33	7.34	7.355	7.33	7.37	7.29
FFA	7.31	7.33	7.35	7.32	7.32	7.35	7.325	7.35	7.30
FFV	7.285	7.31	7.32	7.32	7.32	7.31	7.29	7.325	7.24

was identified and exteriorized the inguinal region incised and the femoral artery and vein isolated Polyethylene catheters were inserted into both vessels their tips advanced to the level of the upper abdomen and they were secured in place The fetal inguinal incision was repaired the leg restored to the uterus and the fetus still within the uterus was rotated through 180° The fetal head was exteriorized the right carotid artery isolated through a ventral midline neck incision and a polyethylene catheter was inserted and fixed in the right carotid artery so that its tip lay in the ascending aorta The neck incision was repaired and the head replaced into the uterus A polyethylene catheter was inserted into the uterine cavity and the maternal abdominal walls were closed Lost amniotic fluid was replaced by 40 ml of warm saline injected through the intrauterine catheter

The mothers were next placed on their side The catheters passing from the blood vessels of the mothers and fetuses were attached to Statham pressure-sensitive transducers and the blood pressures and heart rates of the mothers and fetuses and the intrauterine pressures were recorded on a Brush multichannel polygraph Small blood samples (0 4 ml) were periodically withdrawn from all theters and analyzed for pH PO_2 and PCO_2 using the trup apparatus (Radiometer Copenhagen) Accuracy analysis was reliable with a maximum variance of 1.5%) *The fetal catheters were so located as to provide* samples of blood of the composition which normally supplies the head (withdrawn from the carotid artery catheter) and the body (withdrawn from the femoral artery catheter) Fetal blood volume was maintained by replacing all blood withdrawn by equivalent volumes of maternal blood The procedures used in animal preparation have been described elsewhere (1)

The mothers breathed spontaneously throughout the period under investigation A 3 litre clear plastic bell was placed over their heads and alternately flushed with 100% oxygen and with room air—30 min each At the end of each period of oxygen or air breathing blood was withdrawn from all maternal and fetal sample sites Thus two sets of PO_2 and pH values of mothers and fetuses from all sample sites were compared each hour—one set was obtained while the mothers were breathing 100% oxygen and the other while they were breathing air The repeated blood sampling during alternate oxygen and air breathing for up to 6 hours permitted fetal oxygenation to be followed at times when the mothers were successively under 1) deep anaesthesia and 2) early and 3) late [illegible] emerged from anaesthesia 4) while nearly awake [illegible] strained on the operating table and 5) after [illegible] of anaesthesia with pentobarbital injection, 30 [illegible] Only those periods were evaluated during which the femoral arterial blood pH values remained above [illegible] This stringent restriction ensured that all values [illegible] reflect findings obtained from metabolically intact [illegible]

In three of the pregnancies oxygen-sensitive [illegible] were utilized to continuously record the oxygen [illegible] fetal tissue The 3 mothers and fetuses were prepared [illegible] described above and in addition miniaturized Clark needle electrodes (outside diameter=0.5 mm [illegible] inserted 1–2 cm into the subcutaneous tissue of the [illegible] the fetus just before head reinsertion. The leads for [illegible] electrodes were connected to a Radiometer PO_2 [illegible] ing module (Digital Acid-Base Analyzer-PHM[illegible]) [illegible] output was monitored on a Brush polygraph channel [illegible] with blood pressures and heart rates of mothers [illegible] fetuses and intrauterine pressure The electrodes [illegible] calibrated just prior to tissue insertion by adjusting [illegible] meter settings with the electrodes alternately placed [illegible] Radiometer PO_2-zero solution and in water saturated [illegible] air All tissue PO_2 measurements were carried out [illegible] 45 min of the last electrode calibration During the [illegible] electrode studies the mothers breathed either 100% [illegible] *ygen or room air for 2–6 min at a time* Alterations [illegible] oxygen tensions in the fetus were continuously [illegible] as they were recorded on the polygraph The abrupt [illegible] and termination of oxygen breathing by the mothers [illegible] permitted the time lag in the elevation or the reduction [illegible] the fetal tissue PO_2 to be determined within the limits [illegible] imposed by the time constant of the measuring system

RESULTS

The effects of depth of maternal anaesthesia on [illegible] magnitude of oxygen transfer to the fetuses [illegible] specifically studied in the present investigation [illegible] The mothers were first anaesthetized with [illegible] pentobarbital 35 mg/kg Then they were permitted to awaken over the next 3 hours After study [illegible] fourth hour while nearly awake they were [illegible] fully anaesthetized and followed during a final [illegible]

PO_2 Determinations in maternal and fetal blood during oxygen and air breathing

maternal femoral artery MFV=maternal femoral vein FCA=fetal carotid artery FFA=fetal femoral artery
etal femoral vein

	Deep anaesthesia						Semi awake		Deep anaesthesia	
	100% O_2	Air	100% O_2	Air	100% O_2	Air	100% O_2	Air	100% O_2	Air
	450	93	420	89	470	80	370	83	290	91
	53	51	57	52	65	45	47	41	69	53
	34	28.5	33	22	27	25	20.5	19	25.5	16
	28	24	23	18	23	21	17.5	16	21.5	16.5
	21	18	17	12	14	13	8.5	8.5	–	12

oxygen tension of fetal blood samples varied a wide range during the 5–8 hours of study and be related to the depth of anaesthesia of the rs However it also varied in relation to the on of the study itself and to a number of other les Because of the multiplicity of factors affected oxygenation of the fetuses compari of oxygen values obtained from different ani at different times were not practicable None ss the general findings obtained with the vari- animals *in the present study accord with the* igs observed on many other animals followed her studies both with respect to trends of the ge observed and with respect to the absolute – of these changes Because of this overall istency of results the findings obtained with a mother–fetus pair (mother 790H) are pre d as representative of the findings obtained all animals

value of a fetal blood sample serves as a able indicator of the respiratory and metabolic of the fetus at that time As long as the mater and fetal blood pH values remain within their mal ranges it may be inferred that the fetuses are her retaining carbon dioxide nor releasing amounts of lactic acid Table I presents pH values of blood samples taken from the ous sample sites *of mother 790H and her fetus* very stage throughout the study As can be these values generally remained within their mal ranges Thus whatever the changes brought ut in oxygen tension of the fetus in this study y were never sufficient to lead to metabolic dis ances

The initial and terminal arterial blood pH values mother 790H were 7 40 and 7 47 Thus this ther maintained her arterial blood pH values re vely constant throughout the study except when she was nearly awake when the pH augmented to 7 49 due to hyperventilation The initial and final maternal femoral vein blood pH values were 7.35 and 7 44 These values were generally about 0 03 units lower than were the values of samples drawn from the femoral artery The initial and final pH values of *blood* taken *from the fetal* carotid artery were 7 32 and 7 31 Again throughout the study the fetal carotid artery blood pH remained about 0 01 units higher than the pH of blood sampled from the *fetal femoral artery Similarly the fetal femoral* artery blood pH remained about 0 02–0 03 units higher than the pH observed in fetal femoral vein blood

The oxygen tensions of blood samples taken from the various blood vessels of mother 790H and her fetus are detailed in Table II and the values obtained from the various sample sites of the fetus are illustrated in the bar graphs of Fig 1 The PO_2 values of the maternal arterial blood when the mother was breathing room air generally fell within the range 90–95 mmHg and when she was breath ing 100% oxygen within the range 410–490 mmHg Thus mother 790H adequately ventilated her lungs whatever her depth of anaesthesia Paradoxically as mother 790H emerged from anaesthesia the PO_2 values of her arterial blood *lowered both when she breathed oxygen (to* 290–370 mmHg from 420–450 mmHg) and when she breathed room air (to 80–83 mmHg from 91–93 mmHg) Furthermore these depressions in arterial blood PO_2 occurred despite heightened respiratory efforts When 790H was nearly awake the oxygen tensions measured in venous blood also decreased by 6–10 mmHg as did the PO_2 values of blood sam ples taken from all sites of the fetus

The blood sampled from the maternal inferior vena cava (through the femoral vein catheter)

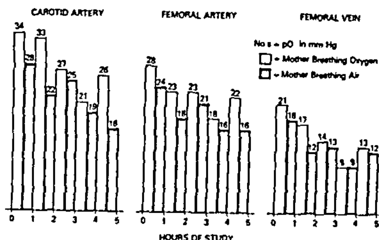


Fig 1 Bar graphs showing oxygen ... of successive blood samples taken from carotid and femoral arteries and femoral vein of the term fetus of monkey ... times when she was alternately bre... 100% oxygen and room air for 30 m... over a 5 hour period

showed considerably higher PO_2 values than did blood sampled from any fetal site at all sample times The average difference in PO_2 value of maternal vena cava blood and of carotid artery blood of fetus was 28 (range = 19–43) mmHg The magnitude of this difference varied during the experiment and tended to be largest when the mothers were deeply anaesthetized and smallest when they were awake In addition the PO_2 values of all fetal blood samples generally declines during the study Thus as can be seen from Table I and Fig 1 the PO_2 value of the carotid artery blood of the fetus of 790H lined from 34 to a final 26 mmHg when sampled ng 100% oxygen breathing and from 28 to 16 Hg when sampled during room air breathing Similar decreases in PO_2 were observed in blood samples taken from all other fetal sites i e the fetal femoral artery blood PO_2 declined from 28 to 22 mmHg during 100% oxygen breathing and from 24 to 16 mmHg when the mother breathed room air and the fetal femoral vein blood PO_2 declined from 21 to 13 mmHg during 100% oxygen breathing and from 18 to 12 mmHg when the mother breathed room air A large decrease in PO_2 of fetal blood samples took place during the second hour of the experiment This decline was observed first in the posterior circulation of the fetus i e in the femoral artery and vein blood samples and later in the circulation to the head (in carotid artery blood samples)

The lowest PO_2 values of fetal blood samples generally occurred when the mothers were semi awake on the operating table At this time the ... values of blood samples taken from the car... artery femoral artery and femoral vein of the fe... of the mother 790H with the mother breathing ...ygen were 21 18 and 9 mmHg and with her breath... ing room air 19 16 and 9 mmHg respectiv... After the mothers were reanaesthetized the ... values of all fetal blood samples elevated In ... fetus of monkey 790H the early PO_2 eleva... observed after the mother was reanaesthe... were 4–5 mmHg In other fetuses these ... were usually larger (as great as 8–10 mmHg ... The improvement in the oxygenation of th... fe... 790H largely disappeared by the time of the sec... sampling (after 1 hour)

The fetal carotid artery blood samples regular... showed higher PO_2 values than did samples ta... from the femoral artery The average differe... through the experiment was 4 2 mmHg However ... this difference was larger early during the st... (when it was 6–10 mmHg) than at the end (whe... was 0–4 mm) The final samples examined show... no differences in PO_2 value between carotid ... femoral artery blood At this time oxygen trans... from the mother to fetus was greatly reduced ... the PO_2 values of all fetal blood samples w... greatly depressed

The differences in PO_2 value of fetal blood sa... ples when the mother was breathing oxygen ... compared to those when she was breathing ai... different times during the study are illustrated ... Fig 2 as they were observed in mother 790H ...

tus At the time of the first comparison sub- on of oxygen for air breathing caused the PO_2 il carotid artery femoral artery and femoral lood to augment by 6 4 and 2 mmHg respec When the same values are compared during ird and fourth hours as the mother emerged anaesthesia and early during the fifth hour she was largely awake the corresponding s were 2 2 and 1 −4 −4 and −4 and 2 2 mmHg respectively Subsequently after the ner and her fetus were reanaesthetized sub- of oxygen for air breathing caused these s to again augment to 7 6 and 4 and 10 6 and nHg respectively In interpreting the differ s in arterial blood oxygen values of the fetus at ent times it is important to bear in mind that ntervals over which the mothers breathed ox and room air from one sample time to another long (30 min) This time length is of sufficient tion that substantial physiologic changes may r both to mother and fetus and these changes alter the base line serving for comparison from interval to the other In fact substantial iges in physiologic state of the mothers and ses are expected in the present study since such iges were purposely induced by first injecting sthetizing doses of pentobarbital into the her by permitting the mother to emerge from sthesia and finally by reintroducing deep sthesia in the mother by injecting additional tobarbital These rapid and marked changes in iologic state which themselves led to marked rations in oxygen transfer to the fetus had the ct of distorting the bars of the bar graphs il rated in Fig 2 Thus when oxygen transfer to fetus was rapidly reduced due to physiologic nges in the mother during a 30 min period when mother was breathing oxygen comparisons of new fetal blood oxygen values with the values ained during the preceding period when the ther was breathing air leads to artifactual reduc ns in the magnitudes of the differences in the PO_2 tal arterial blood under the two conditions of s breathing This effect was so prominent early ring the fourth hour as the mother awakened that led to negative difference values when comparing tal PO_2 values with the mother breathing oxygen d room air (see the reduced PO_2 values in blood mples as taken from all sample sites of the fetus rly during the fourth hour when the mother was eathing oxygen compared to the preceding period

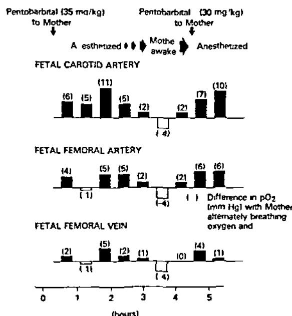


Fig 2 Bar graphs showing the magnitudes of the increases (or decreases) in PO_2 of blood sampled from the carotid and femoral arteries and the femoral vein of the term fetus of monkey 790H when she was breathing oxygen as compared to when she was breathing room air alternately for 30 min each over a 5 hour period Negative values occurred when large physiologic changes took place in the mother or the fetus during a single 30-min interval when the mother was breathing oxygen leading to marked decreases in oxygen tension of fetal blood samples i e during that time when mother 790H awakened from anaesthesia when all samples of fetal blood showed marked decreases in oxygen tension

when she was breathing room air) Similar effects but of opposite sign were observed when marked alterations in oxygen transfer to the fetus occurred during periods of air breathing

Fetal subcutaneous tissue PO_2 was measured continuously using oxygen sensitive electrodes When the mothers breathed 100% oxygen the oxygen tension of the fetal subcutaneous tissue increased by as much as 5 mmHg as illustrated in Fig 3*a* and *b* These increases in tissue PO_2 were regularly delayed by about 50 sec after the mother started oxygen breathing The tissues then required another 30–150 sec to reach their maximum oxygen values Then after the mothers were abruptly shifted to air breathing the fetal tissue oxygen tension continued unchanged for another 40–60 sec before it began to decline and 100–180 sec more were required before the oxygen tension returned its earlier value

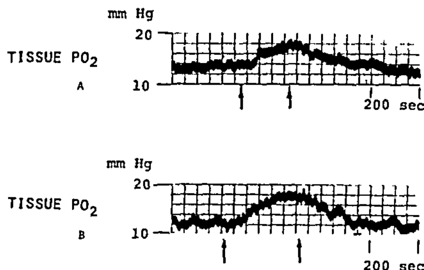


Fig 3 Changes in oxygen ten... cervical subcutaneous tissue f... full term monkey fetus following oxygen administration to the ... for 3 min 10 sec (*a*) and 5 min ... (*b*) The mother was breathing spontaneously during the en... period of recording

DISCUSSION

When pregnant rhesus monkeys were switched from air to oxygen breathing comparisons of PO_2 values of samples of fetal blood as taken from all sites showed increases in oxygen tension in almost all instances In those few occasions when such increases were not observed the physiologic state of the animals had changed sufficiently over the 30 min intervening between samples that the actual oxygen transfer to the fetus had diminished to an extent greater than the magnitude of the oxygen increment brought about by maternal oxygen breathing In other unpublished studies fetuses sampled immediately before and after oxygen as administered to the mothers always showed reased oxygen values at all sites in all in ces during the period of oxygen breathing That oxygen administration to the mother leads to increased oxygenation of the fetus is also evident from the present results obtained with the oxygen sensitive electrode in fetal tissue

The extent to which oxygen breathing by the mother increased oxygen values of the fetus varied with the physiologic state of the mother and the fetus These increases were largest when the mothers were anaesthetized and least when they were nearly awake and in a stressed state on the operating table Furthermore when the mothers were awake and the PO_2 values of all fetal blood samples were abnormally depressed reinstitution of anaesthesia restored all of the fetal blood PO_2 values towards normal and increased the extent to which oxygen administration to the mother improved oxygenation of the fetus

The increased oxygen transfer to the fe... brought about by oxygen breathing by the mo... can be understood by considering the changes ... maternal oxygen breathing produces in the oxy... sition of maternal arterial blood When the PO_2 ... maternal arterial blood falls within the range 9... mmHg as occurs when she breathes room air ... hemoglobin contained within red blood cells ... nearly fully saturated (>96%) When the arter... blood oxygen tension is then increased to 4... mmHg as occurs during oxygen breathing t... quantity of oxygen transported bound to hemog... bin is increased by only 0 8 vol% or by 4% of the total oxygen transported at normal oxygen te... sions At the same time the quantity of oxyg... transported in physical solution which at norm... oxygen tensions corresponds to 0 3 vol% or 1... of all oxygen carried increases to 1 9 vol% or ... of all oxygen carried when the mother is breathin... oxygen Thus oxygen breathing by the mother increases the quantity of oxygen carried in the blood both bound to hemoglobin and especially carried in physical solution The magnitude of these increases taken together is 2 4 vol% which mea... the mother s blood carries 12 2% more oxyg... when she breathes oxygen than when she breathe... room air About 60–70% of this increased oxyg... carrying capacity of blood brought about by oxyge... breathing comes about as additional amounts ca... ried in physical solution The effects of oxyge... breathing on oxygen transport by blood have bee... more fully discussed by others (11)

The effectiveness of oxygen breathing in increas... ing the quantity of oxygen actually transported b...

nal blood is greatly increased in those circum s when the oxygenation of the maternal blood pressed below normal to start with Such emia is not uncommon and may occur as a quence of maternal respiratory depression a variety of pulmonary diseases Use of thetic agents or narcotics at high dose levels diminish maternal arterial blood oxygenation pressing the mother s respiratory state while nonia asthma emphysema or other pulmo- diseases decrease actual oxygen delivery to rculating maternal blood When oxygen ned air is administered under any of these the maternal arterial blood oxygen nt *is increased by amounts far greater than* presently described Thus administration of n to women in labor where respiration is de- ed or pulmonary function is altered leads to far r improvements in fetal oxygenation than did administration of oxygen in the present study e the oxygen tension of maternal arterial blood maintained *within normal range during the* ods of air breathing

veral factors in addition to oxygen content of rnal arterial blood affect net oxygen transport maternal to fetal blood stream The blood sure of the mother by determining the volume of blood through the intervillous space im antly influences the quantity of oxygen de ed to the fetus Thus when the mean blood sure of pregnant rhesus monkeys was rapidly ced from a normal of 90–100 to 50 mmHg the arterial blood PO_2 decreased from 30 to 20 Hg (13) The magnitude of such decreases in l arterial blood PO_2 brought about by lowering ood pressure in the mother may be sufficiently it as to cause fetal brain injury or death (3) Use arbiturates at dose levels sufficient to cause ificant reductions of maternal blood pressure ilarly decreases oxygen tension in the fetal rnal blood These latter effects of deep pen arbital anaesthesia can be reversed in every ance by restoring the blood pressure of the ther to normal

Another factor which importantly influences ox n transfer to the fetus is the state of tonus of the rine blood vessels The many factors which alter rine vascular conductance have been reviewed detail elsewhere (2) and will not be discussed ther here However the important role played uterine blood vessel tonus in determining oxygenation of the fetus is well illustrated in the present study During the mother s emergence from anaesthesia the oxygen tension of the maternal arterial blood and the maternal blood pressure were both well maintained or indeed sometimes elevated Despite this the supply of oxygen to the fetuses regularly declined to low levels as was demonstrated by the marked reductions of blood oxygen pressures at all sample sites Under the same circumstances the magnitudes of the increases in fetal blood PO_2 observed when oxygen was administered to the mothers also declined to low values indicating a decreased effectiveness of oxygen breathing in ameliorating asphyxia of the *fetus under conditions of maternal stress These de*creases in fetal blood PO_2 at all sample sites due to diminished oxygen transfer to the fetus with stress of the mother can only be explained by assuming a decreased uterine artery blood flow and thereby a reduction in maternal blood flow through the intervillous space

The oxygenation of the fetus was most profoundly depressed when the mothers were awake and restrained Earlier studies have shown that stressing pregnant rhesus monkeys psychologically leads to diminished oxygenation of the fetuses (15) The decreases in fetal arterial blood PO_2 typically developed 50 sec after the psychologic stress was applied to the mothers and fetal oxygenation improved usually within minutes after stress was removed These results indicate that maternal anxiety or fear can reduce oxygen transfer to the fetus Such reduced oxygen transfer to the fetus has been explained as due to increased maternal sympathetic nervous system activity constriction of blood vessels supplying the uterus and other visceral organs and reduced oxygen delivery to the fetuses A similar action seems likely here to account for the marked reductions of fetal arterial blood PO_2 as the mothers roused from anaesthesia That the oxygen tension of fetal blood samples inevitably augmented after these mothers were reanaesthetized supports this suggestion The effects of catecholamine infu*sions in diminishing oxygenation of the fetus have* already been described elsewhere (1 8 9 16) and will not be further discussed here

Significant decreases in PO_2 were observed in fetal blood samples in the present investigation during the second hour of study These decreases appeared first in femoral and only later in carotid artery samples The declines occurred at

when the mothers were still fully anaesthetized and their physiologic states stable Though the mothers experienced some decreases in blood pressure at the same time these blood pressure decreases were not sufficient to lead to diminished oxygen values in fetal blood Rather the reductions in fetal oxygenation more likely resulted from physiologic changes taking place in the fetuses themselves since the reductions did not appear simultaneously at all sample sites but rather appeared first in samples taken from the posterior circulation The relations of these early diminutions in oxygen tension in fetal blood samples to the further decreases which develop as the hours pass remain unclear However both the early and late declines need be distinguished from the superimposed changes in fetal oxygenation that occur as a result of changes in level of anaesthesia of the mothers The basis for the apparently inexorable declines in fetal oxygenation which take place in rhesus monkeys during prolonged barbiturate anaesthesia remain entirely unknown Whatever the basis for these changes may be their eventual understanding is critical to any efforts to find methods of treatment for intrauterine asphyxia of the fetus

Fifty sec were required for the oxygen tension in fetal tissue to start to increase after the mothers began oxygen breathing A similar lapse of time was required for the fetal tissue oxygen tension to begin to decline after the mothers were returned to air breathing Such delays are entirely expected since the minimum time required for oxygen tension in tissue to respond one way or another is that the time required for the maternal blood to circulate from the pulmonary alveolar capillaries to the left side of the heart and through the aorta and uterine blood vessels to the placental intervillous space This circulation might be expected to take as long as 20–30 sec in the deeply anaesthetized monkey An additional 20–30 sec is then required for fetal blood to absorb the added (or reduced) oxygen from the intervillous space and to transport it back from the placental villous capillaries through umbilical veins to the inferior vena cava and through the left side of the heart and ascending aorta to the subcutaneous tissues of the neck The elapsed time of 50 sec for changes in fetal tissue oxygenation to appear after oxygen administration to the mother also compared closely with the 50 sec delay which are observed after the mothers are psychologically stressed and the fetuses begin to show decreases in oxygenation (15) Though the mechanisms sponse in these 2 circumstances differ in tails the times required for their respo lar The short time required for fetal blood from the villous capillaries to the fetal neck agrees with the 10–20 sec minimum delay encountered between the beginning of a contraction and the first appearance of a decre the heart rate of the fetus (late deceleration) (1

Oxygen electrodes as presently construct subject to considerable technical prob amongst these the consumption of oxygen (The degree to which this oxygen consumpt fects the oxygen tension measured is diffi estimate since the magnitudes of changes in tension induced in the vicinity of the electrode depends on its distance from nearby capill In turn this distance varies from one electrode sertion to another and from one time to an during single insertion Other sources of system error in oxygen measurement include diff in geometry of electrodes in characteristic membranes utilized and in diffusional and tional properties of surrounding tissue

The characteristics of local blood flow may alter as a result of trauma during electrode in tion If a hematoma forms around the electrode it may affect blood flow in the vicinity electrode membrane may also become coated fibrin causing changes in PO_2 measurement Sin is not possible to predict the magnitudes of the various errors frequent calibrations of electr are necessary Measurements carried out electrodes left in position for long periods w calibration are therefore questionable Van sources of error related to electrode construc alterations induced in tissue by electrode inse have been discussed by Grunewald (6)

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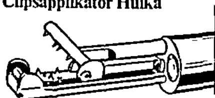
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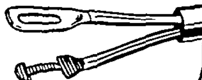
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QUANTIFICATION OF FETAL HEART RATE VARIABILITY IN RELATION TO OXYGENATION IN THE SHEEP FETUS

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act Beat-to-beat variability has been suggested as a ve indication of fetal well-being The suggestion pates from case reports of observed decrease in var ty preceding clinical signs of fetal asphyxia and fetal 1 Against this background a study was performed to late possible changes in heart rate variability in rela to changes in fetal oxygenation Chloralose thetized sheep were used Short term hypoxia was uced without acidosis The FECGs were recorded on netic tape and later analysed by scrutinizing each QRS plex prior to the trigger of a rate meter The differen index (DI) described by Yeh and co-workers was en because it is easily computed and reflects the ibility of coefficient of variation for two successive intervals In contrast to the generally held view of a ressive diminution of variability during the develop- t of asphyxia the variability was found to increase llel with a decrease in fetal arterial PO_2 determined on d samples withdrawn at intervals and ranging between nd 10 mmHg The correlation between variability and in the range below 8–10 mmHg is still to be deter ed

INTRODUCTION

e diagnosis of impending hypoxia is usually made er interpretation of the simultaneous recording heart rate and intra uterine pressure Thereby adycardic episodes following uterine contrac ns at defined intervals are considered to reflect w oxygen availability and to represent a hazard s situation for the fetus Bradycardia as a conse ence of hypoxia is however a late sign (11) erefore other parameters are sought which ght change characteristically within higher ranges oxygen tension The differences in duration be een consecutive heart cycles have been proposed as a suitable parameter for this purpose (1 6 7 8 9 14)

Hammacher 1966 (5) introduced the concept of oscillation amplitude as a means of expressing heart rate variability in quantitative terms The alteration in argument following the plotting of consecutive heart cycle lengths against each other in a two-dimensional system according to de Hahn (3) and the differential index of Yeh (15) serve the same purpose All these three indices describe short term variability The generally accepted view is that this variability is high when the fetus is in a relatively undisturbed condition but decreases when the oxygen supply is reduced

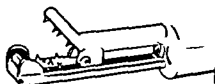
The present study was undertaken to evaluate possible changes in heart rate variability related to changes in fetal oxygenation An animal experimen tal model was used in order to make possible re cording of fetal ECG during graded hypoxia without the interference of severe acidosis An additional purpose was to establish the relationships between fetal heart rate variability during hypoxia and other cardiovascular parameters such as arterial blood pressure fetal ECG pattern and cardiac contrac tility

The ultimate goal of the study would be to ascer tain which variables contain most information about impending oxygen lack to the fetus

MATERIAL AND METHODS

The experiments were conducted on 8 ewes of mixed breed with 11 fetuses The gestational ages ranged from 123 to 140 days (term 147 days) The gestation was either

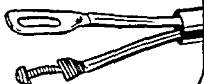
1 Clipsapplikator Hulka



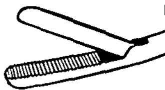
2 Ringapplikator Lay



3 Bipolar griptång



4 Endotherm griptang, teflonbelagd



WOLF
laparoskop Palmer



NYHET

LUMINA SL-optik
Ljusare, större upplösningsförmåga Raka laparoskopoptiker, 10, 7 och 5 mm

WISEX

Kirurgiska Instrument AB Wisex, Box 2009, 431 02 Mölndal, Tel 031/81 00 55, 81 00 2

71 72 73 74 75 pH

Scattergram of D I values correlated to pH

RESULTS

orrelation between arterial PO_2 determined
ood samples from the right brachial artery of
uses and the corresponding D I value is vis
d in the scattergram (Fig 1) There is a lack
ormation regarding the relationship between
and D I in the range below $aPO_2=8$ mmHg
egression equation is therefore based on the
rvations between 10 mmHg and 26 mmHg The
f regression of D I on aPO_2 has the equation
3−1 7x The correlation coefficient is −0 78
11 $p<0\ 001$ The 95% confidence limit of the
ssion line is minimum ±2 08
e relation between pH and D I is shown in
It is observed that the majority of the obser
ns are distributed between pH 7 20 and pH
Only 8% of the observations fall below 7 17
observations within the range 7 20–7 42 are
omly distributed
terations in different cardiovascular functions
arterial pressure (MAP) left ventricle
ardial contractility (max dp/dt) fetal heart
(FHR) fetal heart rate variability (D I) and
ressive changes in the S T interval of the fetal
are plotted together with aPO_2 and pH against
in Fig 3 The values in the figure were
ined from three fetuses subjected to varying
ees of hypoxia without acidosis
he general tendency seen in the cardiovascular
onse to hypoxia is some increase in MAP and
The increase in max dp/dt value might indi
an increase in myocardial contractility as a

response to hypoxia Thus there are no signs of failing myocardial function associated with early increase in fetal heart rate variability and the ap pearance of ECG changes In case A a decrease in D I was noted after 30 minutes of hypoxia ($aPO_2=6$ pH=7 27) The values were obtained at the beginning of the functional failure of the cardiovascular system as demonstrated by a fall in maternal arterial pressure FHR left ventricular myocardial contractility and maximal changes in the ECG

DISCUSSION

In the endeavour to detect developing fetal hypoxia interest has been focused on the variability of fetal heart rate Originally the variability was discussed on the basis of phonocardiograms (5) but subse quently ECG signals were used to trigger heart rate meters Along with development in electronics true beat to-beat recordings were made available and the synonymous description has been instantane ous FHR recording or the use of non averaging systems

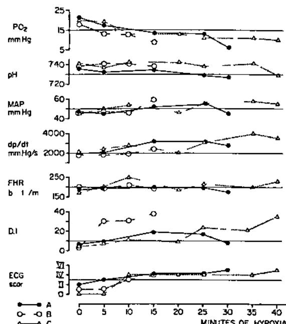


Fig 3 The relationship between aPO_2 pH and various cardiovascular parameters mean arterial pressure (MAP) myocardial contractility (max dp/dt) fetal heart rate (FHR) heart rate variability (D I) and ECG score during continuous hypoxia in three mature sheep fetuses

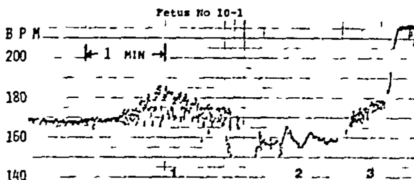


Fig 4 Change in variability [illegible] ing progressive development [illegible] poxia. *1* Marked variability [illegible] duced variability associated [illegible] aPO_2 value of 6 mmHg *3* [illegible] restitution.

In the usual FHR recording the beat to-beat variations are difficult to quantitate Hammacher (6) has introduced the term oscillation amplitude and subdivided the oscillation range in 3–4 subgroups de Hahn (3) has described the short term variations from vector analyses of consecutive heart cycle lengths while Yeh (15) has described the differential index used in this study In the D I the consecutive cycle length differences are related to the actual mean level of two heart cycles each *d* is proportional to the coefficient of variation for consecutive heart cycle lengths Similar indices can be constructed in several modifications but it is likely that the information gained in this respect would not be much improved

The general concept regarding the heart rate variability is that its index value is large in the situation f fetal well-being and decreases in proportion to terioration until a "silent pattern" is seen (1) It is therefore contrary to expectation to find that under the circumstances of this study the D I values increase along with the diminution of PO_2 until a PO_2 level of 10 mmHg is reached It remains to be seen whether or not the index values are correlated to PO_2 in the range below 8–10 mmHg A sufficient number of observations within this low range has not hitherto been obtained The clinically observed situations of "silent pattern correlated to poor fetal outcome might represent a PO_2 value in an even lower range

When comparing other variables reflecting the status of the fetus it appears as if the increase in the D I is associated with a still preserved circulatory function as judged from the behaviour of MAP FHR and max dp/dt in the cases analysed in Fig 3 The increase in D I seems to be associated with the anaerobic utilization of myocardial glycogen since alterations in the S-T interval of the fetal were recorded at the same time These changes have in previous studies been shown a sign of myocardial glycolysis during hypoxic stress (12 13)

In this study the ultimate decrease in fetal rate variability was induced around 8-10 Acidosis was not present however and [illegible] drugs had not been administered The level of [illegible] ygen pressure associated with the decrease in [illegible] during clinical situations needs to be elucidated further

The present study has some drawbacks [illegible] the use of anesthetized animals even if [illegible] is stated to be the ideal anesthetic agent for study of cardiovascular reflexes (4) and the [illegible] continuous oxygen tension determination. A preliminary report by Dalton and co-[illegible] points in the same direction however (2) The authors found that hypoxemia in chronic [illegible] anesthetized sheep fetuses caused a large [illegible] sustained increase in heart rate variation [illegible] either as the S D of the heart period or as the [illegible] beat to-beat difference

In the future elucidation of the problem a tech[illegible] que must be developed enabling one to [illegible] actual heart cycle length with the simultaneous [illegible] value derived from continuous recording of [illegible] means of an indwelling arterial or a transcut[illegible] ously applied oxygen electrode Various [illegible] sites and electrode placements must be tested [illegible] order to investigate a possible time difference [illegible] tween the actual PO_2 and the change in heart [illegible] length It would have been of considerable [illegible] for example to determine the temporal rel[illegible] between the gradual development of hypoxia [illegible] the induced change in variability in the [illegible]

r 10–1 The dynamics of the progressive es in beat to-beat variability along with al deepening hypoxia in this case is shown in

CONCLUSIONS

1 acidotic exteriorized term sheep fetuses of …lose anesthetized mothers the variability of heart rate expressed as differential index was … ely proportional to fetal arterial PO_2 within …nge of 10–26 mmHg This observation is in …adiction to the generally held view and needs …boration in further extended studies using a …y of species and including determination of …bolic parameters

ACKNOWLEDGEMENTS

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STILBESTROL ADMINISTRATION IN THE PUERPERIUM AND ITS EFFECT ON THE PROLACTIN EXCRETION OF NON LACTATING PATIENTS

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Miriam Kaufman and David M Serr

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The Institute of Endocrinology (Head B Lunenfeld) Tel Hashomer Israel

act The relationship between stilbestrol treatment placebo treatment was studied in 2 groups of non ng patients Plasma prolactin levels were evaluated in 2 groups on day 1 3 and 7 of the treatment by a immunoassay technique with the double antibody od using Serono hPRL kit Our results show that ctin values increased significantly in the stilbestrol and decreased in the placebo group It seems the main reason for the drying up of milk" is the of stimulation of the nipples which after a relatively tant time of 5–10 days will lead to decreased prolactin s Stilbestrol treatment is not effective in drying up nilk more rapidly in patients who do not want to When patients have symptoms a combination of gesia and breast support usually brings relief within 24 hours

maternal ability to secrete milk depends on quate proliferation of mammary glandular tissue ducts during pregnancy This proliferation is ulated by the increase in estrogen proges ne and lactogen After parturition prolactin is an important and major part among other mones in initiating milk secretion by its ogenic activity and in maintaining milk produc by its galactopoietic action (1 2)

Jnlike other pituitary hormones which are se ted following stimulation from the hypo lamus prolactin is inhibited by the influence of Prolactin Inhibitor Factor (PIF) This therefore ans that the release of prolactin is continuously pt in check and that substances which decrease PIF levels act by the withdrawal of inhibition ich results in increased prolactin secretion Vari s investigators have also shown that the suckling lex leads to an increased release of prolactin Thus the infant by suckling activates the nerve receptors at the base of the nipple and causes the release of prolactin (3) It could be assumed that this reflex is brought about by oxytocin release but this does not appear to be the sole reason as it can be demonstrated that oxytocin does not cause prolactin release in tissue from the rat hypophysis cultured in vitro (4)

When the mother is not nursing suppression of lactation is of importance Although the cessation of the nipple stimulation effect and suckling are of major importance many therapeutic methods have been suggested to shorten and ease the process of "drying up the milk (5 6 7) Most of these treat ments if not all are known to be of questionable efficiency

The development of a reliable and specific radioimmunoassay for human plasma prolactin enabled evaluation of prolactin levels from birth to adult life and especially the values in plasma during the puerperium in nursing and non-nursing mothers (8) It seems to be one of the major hormones con trolling milk formation

This study was undertaken to evaluate various drugs currently in use for the suppression of lacta tion particularly stilbestrol by studying the plasma prolactin levels in non nursing patients

MATERIAL AND METHODS

A total of 18 patients who for various reasons requested to bottle-feed their offspring were considered for this study Two of them were primiparas the 16 others were

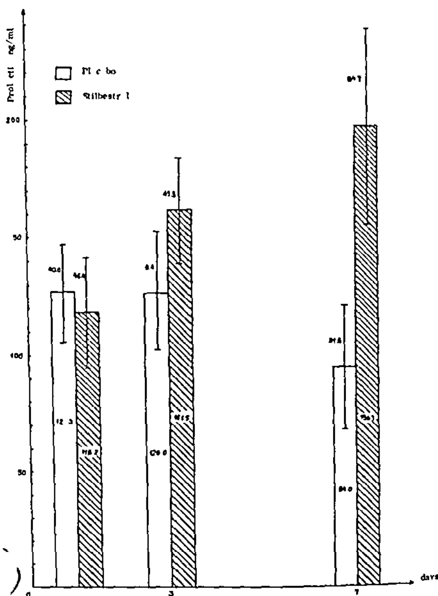


Fig 1 Prolactin levels in nursing mothers treated w placebo or stilbestrol (values given in ng/ml±S D).

multiparas with 2 to 4 deliveries including the present one They all had normal spontaneous deliveries at term

These patients were divided into 2 groups the first group consisting of 9 patients was treated with stilbestrol given orally 3 tablets a day of 5 mg each for 5 consecutive days starting on day one following delivery For the purpose of this study day 1 was calculated as 18 to 24 hours following time of delivery

The 2nd group consisting of 9 other patients were given a placebo consisting of a multivitamin tablet presented exactly like the stilbestrol tablet in shape color and size It was given similarly to the stilbestrol 3 times a day for 5 consecutive days The nurses in charge of drug administration were not informed which of the patients were receiving the stilbestrol tablets or the placebo thus eliminating bias in reporting complaints by the patients about breast tenderness or engorgement milk secretion and fever Recording of these complaints was carried out by the nurse and/or by the resident in charge of the Both nurses and resident were not informed of the fi into the two groups The follow up was continued period of 14 days from the time of delivery and patients were therefore asked to come back e ery following their discharge from the hospital for a check up Both groups were advised to support breasts in a tight and well fitting brassière even for night

Five ml of blood were withdrawn from these p and collected on heparin so as to collect the sup plasma following a 15 min centrifugation at 20 Plasma was then stored in deep freeze

Three samples were collected one day foll win ery on day 3 of the treatment and on day 7 fo delivery Collections of blood were carried out at th time on each occasion

Plasma prolactin values were estimated by

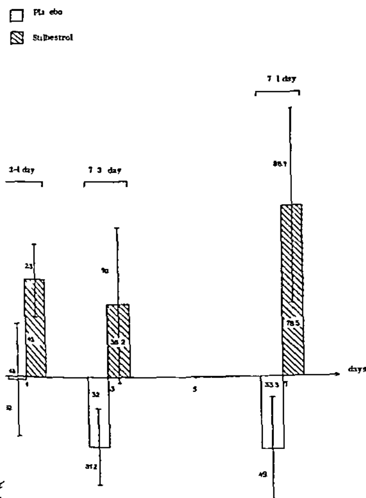


Fig 2 Difference in prolactin levels in non-nursing mothers treated with placebo or stilbestrol (values are given in ng/ml±S D)

...ssay with the double antibody method This ...d uses the Serono technique and their hPRL kit ...nsitivity of this method is about 5 ng/ml

RESULTS

...plasma prolactin values in these two groups of ...nursing patients treated randomly by stilbe... or by a placebo are schematically presented in ... 1 and expressed in ng/ml±S D

...hen the treatment starts with stilbestrol the ... of prolactin of day one following delivery was ...2 ng/ml with a standard deviation of ±46 4 on ...3 following delivery 161.5 ng/ml±47 3 and on ...7 following delivery 196 7 ng/ml±84 7

...the placebo group on day one following delivery prolactin was found to be 127 3 ng/ml±40 0 on day 3 126 0 ng/ml±48 4 and on day 7 following delivery 94 0 ng/ml±51 8

Statistical analysis showed a p value of less than 0 4 for day one between the placebo users and the stilbestrol treated patients p less than 0 1 on day 3 and a highly significant difference on day 7 with p value of less than 0 05

In fact the results showed a significant rise of plasma prolactin levels from day 1 to 7 in the group treated with stilbestrol from 118 2 ng/ml±46 4 to 196 7 ng/ml±84 7 In the group treated with placebo prolactin varied from 127 3 ng/ml±40 0 on day one to 94 0 ng/ml±51 8 on day 7 following delivery which is not significantly different

Fig 2 expresses the difference in plasma pro-

lactin levels in ng/ml in these 2 groups of non nursing mothers Differences were calculated between day 3 and 1 of the treatment 7 and 3 of the treatment and 7 and 1 of the treatment Results were as follows a negative difference of 1 3 ng/ml for the placebo group compared to a positive difference of 43 3 ng/ml in the stilbestrol group between day 3 and 1 with a *p* less than 0 025 which is highly significant Difference between day 7 and 3 was negative in the placebo group to 32 0 ng/ml *and a positive difference of 35 2 ng/ml for the stil*bestrol group with a *p* less than 0 0125 and again a very significant difference between day 7 and 1 with a negative difference for the placebo group of 33 3 ng/ml to a positive difference of 78 5 ng/ml for the stilbestrol group and a *p* value of less than 0 025

As for the clinical results only five of the patients treated with stilbestrol complained of side-effects as compared to 9 patients in the placebo group However the side effects in the stilbestrol patients were expressed as more severe in intensity especially engorgement pain and the discharge of milk compared with slight engorgement in the placebo group No fever was reported in either group

It may be of interest to note that these side effects appeared earlier in the placebo-treated patients than in the group treated with the stilbestrol In the placebo group they started on day 3 while in the stilbestrol group on day 5 to 10

Most of the side effects disappeared 24 to 48 hours after their appearance in the placebo group nd 24 hours to 3 days following their appearance in the stilbestrol group

DISCUSSION

A relatively large group of new mothers do not nurse their babies for various reasons (9) These post partum patients seek constant advice and treatment for the purpose of milk suppression Stilbestrol is along with various other estrogen preparations the drug of choice used for suppressing lactation in many maternity centers These drugs are prescribed and are considered efficient based mainly on clinical observations and reports in the literature (10 11) but in most of them they were carried out with no definite control and with a relatively short follow up Moreover in one clinical study (12) no differences were found in the symptoms of 500 non nursing mothers treated w[illegible] without stilbestrol

Although the hormonal basis of milk produc[illegible] is only partially understood it seems that pitu[illegible] prolactin is of primary importance and the[illegible] can be of use in evaluating treatments [illegible] used for suppression of lactation

Our results stress the fact that plasma prol[illegible] values far from decreasing are actually incre[illegible] significantly when patients are treated with stilbe[illegible]strol *and when compared with patients w*[illegible] ceived placebo treatment It seems that the [illegible] reason for the drying up of milk is the lack [illegible] stimulation of the nipple of the breast which [illegible] its effect after a relatively constant time [illegible] from 5 to 10 days Time is the factor responsible [illegible] the decreased prolactin level in the group of pa[illegible]tients treated with the placebo drug The fact [illegible] stilbestrol increases the plasma prolactin level [illegible] be partially explained by a feedback mechanism [illegible] which stilbestrol reduces the hypothalamic [illegible] of prolactin inhibitor factor

From the clinical point of view these results [illegible] high excretion of prolactin may explain the fact th[illegible] patients treated with stilbestrol will complain [illegible] their symptoms later than in the group treated [illegible] a placebo In the same manner it seems that the [illegible] symptoms and in particular breast engorgement [illegible] tenderness and milk discharge were more [illegible] felt by the stilbestrol treated patients when [illegible] up is continued after the period reported in [illegible] study

From these observations one can conclude [illegible] stilbestrol treatment or other drugs with [illegible] estrogenic effect are not efficient for the [illegible] treatment of stopping milk secretion in p[illegible] who do not want to nurse their babies

In cases complaining of clinical symptoms [illegible] combination of analgesia and breast s[illegible] other local treatments usually bring relief within [illegible] to 48 hours It seems that the time following [illegible] non stimulation of the nipple is among th[illegible] factors responsible for the suppression of lacta[illegible]

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CHANGES OF BONE MINERAL CONTENT DURING PREGNANCY AND LACTATION

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act In order to study changes in the calcium depots body during pregnancy and lactation bone mineral minations were performed on fourteen pregnant en and eighteen mothers post partum by X ray trophotomeyry Pregnant women exhibited a loss in cular bone but not in cortical bone when measured during late first or early second trimester and again week post partum Lactating women who nursed less three months lost mineral during the first three ths and than regained it while those who nursed for r than three months had no losses during six months udy

high incidence of fracture in postmenopausal nen due to osteoporosis constitutes a social and ical problem It is possible that pregnancy can ome extent prevent future postmenopausal os orosis as retrospective investigations using ton absorption techniques indicate an increase one mineral with parity (4 9 10) Moreover iparae seem to be overrepresented among nen with spinal osteoporosis (11)

he purpose of the investigation reported here to determine whether pregnancy and lactation uence the bone mineral content

MATERIAL AND METHODS

Women who in an early stage of pregnancy attended an antenatal clinic were asked to participate in an investigation of bone mineral changes during pregnancy Fourteen women completed the study By means of X ray spectrophotometry the regional bone mineral content was determined in two sites of the forearm The measurements were performed in the late first or the early second trimester and repeated one week after delivery The measuring sites were one and eight cm proximal to the radiocarpal joint representing trabecular and cortical bone respectively

The postpartum period was the subject of a separate investigation Women in a maternity ward were asked to participate in an investigation of bone mineral changes during lactation Eighteen volunteers completed the study Measurements were performed one week after delivery and repeated 3 and 6 months postpartum

Measurements were also carried out on nine non-pregnant and non lactating controls during the same period The post partum women and the controls were questioned about their milk-drinking habits hormone treatment and previous ability to breast feed The measuring sites were situated in the forearm 1 and 8 cm proximally to the radiocarpal joint the femur 20 cm proximally to basis patellae and in tuber calcanei

The bone mineral content was determined by X ray spectrophotometry (5 6) In this method the different

ble I *Age previous pregnancies previous lactation and exposure to contraceptive hormones during the ow up period*

	No of patients	Age in years		Previous pregnancies (Mean)	Previous lactation (No)	Exposure to hormones (No)
		Mean	S D			
trols	9	26	4 7	0 2	1	2
gnant	14	28	4 7	0 9	9	0
tating	18	29	3 1	0 7	11	2

Table II *Bone mineral changes during pregnancy*

	Mean (%)	S D	*P*
Radius+ulna shaft	+2 0	5 5	>0 05
Radius+ulna distal	−4 2	7 0	<0 05
Mean of both sites	−1 1	5 2	>0 05

skeletal parts are positioned in a fluoroscope and scanned with a beam from an X ray tube The beam comprises two wavelengths by means of which the attenuation in the soft tissues surrounding the bone can be compensated for The measuring sites and the measuring precision have been described by Dalén & Jacobson (3)

RESULTS

Details of age previous pregnancies previous lactation and exposure to contraceptive hormones during the follow up period are given in Table I

In the pregnant group the mineral content decreased in the distal measuring site containing trabecular bone (Table II) There was no significant change in the diaphyses of the forearm containing cortical bone

In the postpartum group no systematic difference was found between mineral changes in trabecular or cortical bone Nor was there a difference between weightbearing and non weightbearing parts of the skeleton As seen in Table III where the mean deviation of four sites for each individual is given mothers lactating for less than three months at first ost and then regained bone mineral as compared th controls Mothers lactating for more than 3 nths did not differ from the controls (Table IV)

Two subjects who ceased breast feeding at an early stage took contraceptive pills (Lynestrenol) during the post partum period The bone mineral changes in these women did not deviate from those of the others

No correlation could be detected be changes in mineral content and age number of p vious pregnancies or milk consumption

DISCUSSION

During reproduction changes of hormonal secr and calcium metabolism influence the mineral co tent of the skeleton in some animals In avia preovulatory increase of estrogen induces grow endosteal bone which serves as a calcium rese for the eggshells (7) In mammals estrogen c stimulate bone growth but this does not occur d ing normal reproduction (8) The bone mine changes during lactation have been studied for stance in cattle A low intake of calcium leads reversible mineral losses but during normal cond tions there is a small increase in bone-mineral co tent during both pregnancy and lactation (1

In humans retrospective studies by photon a tenuation techniques indicate an increase in bo mass with parity (4 9 10) Few prospective stud by this technique have been carried out Ch iansen et al (2) found a constant mineral con ent the forearm during pregnancy in thirteen wom and Atkinson & West (1) recorded a loss of ab 2% in the femur diaphyses of ten lactating wo during a period of hundred days

The current view on the mineral changes in wom en seems to be that mineral is stored during pre nancy and lost during lactation (4)

The present study showed a small but significa loss of mineral from trabecular bone during pre nancy and hence the results do not favour th hypothesis that pregnancy leads to an increase bone mass Trabecular bone constitutes ab twenty per cent of the total bone mass but it metabolically more active and reflects changes the calcium metabolism earlier than cortical bone

The finding that mothers lactating for only a sh

Table III *Bone mineral changes in women lactating for less than three months as compared with controls*

		0–3 months			3–6 months		
	No	Mean of four sites (%)	S D	*P*	Mean of four sites (%)	S D	*P*
Lactating	7	−2 6	3 2	>0 05	+9 1	5 0	<0 05
Controls	9	+1 8	4 8	>0 05	+1 7	6 4	>0 05
Difference		−4 4		<0 05	+7 4		<0 05

IV *Bone mineral changes in women lactating for more than three months as compared with controls*

	No	0–3 months Mean of four sites (%)	S D	*P*	3–6 months Mean of four sites (%)	S D	*P*
...ting	11	+1 7	3 7	>0 05	+4 0	3 0	<0 05
...ols	9	+1 8	4 8	>0 05	+1 7	6 4	>0 05
...rence		−0 1		>0 05	+2 3		>0 05

...d lost more bone mineral than mothers lactat... or a longer period was unexpected It is possi... hat some mothers cannot adapt themselves to ...ncreased load on the calcium metabolism and ...therefore not able to breast feed for a long ...d It is also possible that some factors may ...ence both the mineral content of the skeleton the ability to breast feed for instance stress or ...nonal disturbances However the losses were ...rsible and half a year after delivery there was ...lifference in mineral content between controls ...women post partum

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RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM AND SODIUM IN NORMAL PREGNANCY A LONGITUDINAL STUDY

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ract Plasma renin activity the concentration of an -nsin I and the urinary excretion of aldosterone and im were studied longitudinally in 10 healthy pri avidae from the 10th week of pregnancy monthly the 7th puerperal day Plasma renin activity and otensin I levels were significantly elevated throughout nancy and showed maximal mean values at the 10th k gradually returning to the level of nonpregnant ien 7 days after delivery They daily urinary excretion dosterone was also increased throughout pregnancy he mean values showed an increasing trend until 34th k They returned to nonpregnant levels 7 days after very There were no significant changes in the urinary ction of sodium during pregnancy but the mean value lower than in the nonpregnant control group There a significant positive correlation between urinary sterone and sodium values while an almost signifi- negative correlation existed between urinary aldo- one and plasma renin activity suggesting the priority iatriuresis in the regulation of aldosterone secretion ng pregnancy No correlation was found between ma renin activity and urinary sodium excretion values

increase of plasma renin activity and plasma iotensin II concentration during pregnancy is l documented (4 11 21) The level of plasma in substrate increases mainly due to the effect of rogens (5) and progesterone on the liver (22) but sma renin concentration has also been shown to rease (4 29) Plasma aldosterone concentration osterone secretion rate and the urinary excre n of aldosterone are known to rise during preg icy (1 4 30) and near term the excretion may as much as ten times that of nonpregnant women) As a result of the increase of glomerular filtra n during pregnancy the filtration of sodium is also reased about 50% (10) but due to increased ibsorption there is a positive sodium balance dur pregnancy (4)

In the nonpregnant state there is a clear correla tion and interaction between components of the renin angiotensin aldosterone system and this system has an intimate correlation with the body sodium water balance as well (3) However there are few and conflicting reports about these interre lationships during pregnancy Also the regulation of this system during pregnancy is quite unclear (29) To solve these problems more systematically we studied the profiles and correlations of plasma renin activity (PRA) angiotensin I (A I) and urinary ex cretion of aldosterone (U Ald) and sodium (U Sod) longitudinally during and after normal pregnancy

SUBJECTS AND METHODS

Ten healthy primigravidae with a mean age of 24 6±0 5 (S E M) years (range 21–27 years) prepregnant weight 51 9±1 0 (range 49–59 kg) and with a mean weight gain of 12 2±0 8 kg (range 6–14 kg) participated in the study from the 10th week of pregnancy until term The blood and urine samples were collected every 4th week with the last samples taken in the 38th week of pregnancy Samples were also collected in hospital on the 7th puerperal day 27 nonpregnant healthy women with comparable age and weight formed a control group No dietary restrictions were required None of the subjects had treatment with diuretics

The blood samples for the PRA and A I determinations were taken at noon after two-hour fast and the mainte nance of upright position for 4 to 5 hours The 5 ml sample was always withdrawn into a chilled EDTA tube in icewater Plasma was separated in 10 min by a refrigerated centrifuge at +4°C and stored at −20°C until analysis The concentration of angiotensin I in the chilled plasma sam- ple was determined by radioimmunoassay EDTA 8- hydroxyquinoline and dimercaprol were used for inhibi- tion of converting enzyme and angiotensinases The specific angiotensin I antiserum and standard and labelled angiotensin I were obtained from New England Nuclear _

Table I *The mean (±S E M) values of plasma renin activity (PRA) angiotensin I (A I) daily aldosterone (dU Ald) and sodium (dU Sod) excretions in the 10th 34th and 38th week of pregnancy (n=10) on the 7th puerperal day and in the nonpregnant control group (n=27)*

	Pregnancy				
	10th week	34th week	38th week	Puerperal	Non pregn
PRA (ng/ml/h)	27 9±9 9	17 6±2 7	11 8±3 2	1 1±0 2	2 [illegible]+0 3
A I (ng/ml)	1 2±0 2	1 0±0 2	0 9±0 [illegible]	0 6±0 1	0 4 0 1
dU Ald (ug/day)	20 8±4 0	68 6±16 8	51 7±7 1	3 8±0 9	3 7+0 3
dU Sod (mmol/day)	114 0±11 0	108 0±15 0	138 0±15 0	138 0±15 0	156 0+[illegible]

For the PRA the angiotensin I generated by plasma renin in one hour at +37°C at pH 6 0 maleate buffered was determined by radioimmunoassay as above Retaining the plasma samples in ice water until half an hour before centrifugation had no effect either on the AI or the PRA levels in plasma samples

For the determinations of urinary aldosterone and sodium excretion the daily urine was collected in 2 parts between 7 am and 7 pm and between 7 pm and 7 am Free and acid labile glucuronized aldosterone in the urine were determined by radioimmunoassay using first the method of Bayard et al (2) for hydrolysis and extraction and for chromatographic purification the method of Ekins et al (7) Urinary sodium was determined by atomic absorption spectrophotometer (Varian Tectron Model 1100) The intra assay precision (±S D) of 10 samples in the same series was 0 38 for PRA at the level of 4 5 ng/ml/h 0 1 for A I at the level of 1 0 ng/ml and 5 5 for U Ald at the level of 65 7 μg/a day The inter assay precision (±S D) for the PRA in 17 different series was 0 15 at the level of 1 14 ng/ml/h

RESULTS

The noon PRA during the pregnancy is presented in ig 1 The mean PRA in the 10th week is higher p<0 05) than the mean PRA in the 38th week (Table I) All PRA values during pregnancy are higher than the values on the 7th puerperal day ($p<0\ 01$) The mean puerperal PRA is however lower ($p<0\ 05$) than in the nonpregnant control group

The profile of angiotensin I levels (Fig 1) during pregnancy is similar to that of PRA The highest mean value was again found in the 10th–14th weeks of pregnancy and a decreasing trend was found afterwards (Table I) The mean puerperal level of angiotensin I was lower ($p<0\ 05$) than during pregnancy In the control group the level of angiotensin I was comparable with the puerperal level

The day night and 24 hour aldosterone excretions during pregnancy are presented in Fig 2 By the 10th week the mean urinary aldosterone excretion is already higher ($p<0\ 001$) than the puer[illegible] or normal control values In advancing preg[illegible] the excretion of aldosterone increases until the [illegible] week and this increase from the 10th to 34th [illegible] significant ($p<0\ 05$) The mean urinary aldoste[illegible] excretion at all stages of pregnancy are h[illegible] ($p<0\ 001$) than the nonpregnant values and [illegible] 34th week excretion is about 10 times as much [illegible] the nonpregnant state All values of the day ex[illegible]tion of aldosterone during pregnancy are h[illegible] ($p<0\ 001$) than the night values

The urinary excretion of sodium remain[illegible] changed during pregnancy (Fig 3 Tab[illegible] [illegible] similar to the puerperal excretion During the [illegible] pregnancy the urinary excretion of sodium is [illegible] than in the control group ($p<0\ 01$)

The correlation between the PRA and [illegible]tensin I values is significant ($p<0\ 001$) but [illegible] relation was found between the renin-angiot[illegible] system and sodium excretion There is no s[illegible]nificant correlation between individual values [illegible] aldosterone excretion and PRA or angioten[illegible]

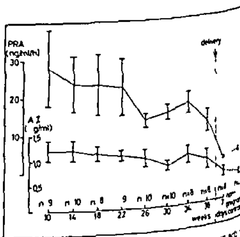
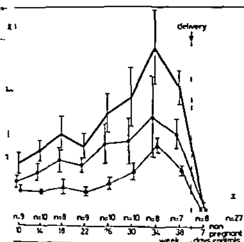


Fig 1 Mean levels (±S E M) of plasma renin act[illegible] (PRA) and angiotensin I (A I) during pregnancy



2 Mean levels (±S E M) of urinary aldosterone ·tion (U Ald) of 12 daytime hours (open circles) 12 ·time hours (open triangles) and 24 hours (thick line) ·ing pregnancy

·re is significant negative correlation be ·en mean values of u Ald and PRA until the ·h week of pregnancy ($p<0.05$) There is a ·tive correlation between the urinary excretion ·dosterone and sodium ($p<0.001$) The correla ·coefficients and the significances are presented ·able II

DISCUSSION

·his study the PRA levels are higher *during preg* ·cy than in non pregnant women and thus accord ·n previous findings (4) The highest values were ·nd in the 10th week of pregnancy and there was ·gnificant decrease towards the end of pregnan This is in agreement with the findings of Weir et ·(30) Robertson et al (19) Tapia et al (23) and ·rdon et al (11) On the other hand a previous ·eral opinion (4) is that the PRA level rises (9) or ·ains unchanged (21) in the course of pregnancy ·il its termination This reflects the difficulties in ·rpreting and comparing the PRA results found ·h different methods in different physical condi ·s In this study all the individual PRA values ·ring pregnancy were above and all the puerperal ·ues below the upper normal limit of 3 7 ng/ml/h ·noon as measured by our method

The level of angiotensin I was also higher in preg ·nt than in nonpregnant women a finding com ·rable with the results of Tapia et al (24) during oral contraceptive therapy The rise of angiotensin I level is probably a reflection of the rise in PRA since A I is an almost inactive intermediate in the formation of the physiologically very potent an giotensin II The level of angiotensin II is also known to increase during pregnancy (11 15 29) but the profile of its secretion and its interactions are not known The profile of A I levels during pregnancy is similar to the profile of PRA and the levels during pregnancy are in a significant positive correlation

For aldosterone secretion during pregnancy there are different profiles reported Weir et al (30) found maximal plasma aldosterone values in the 16th week of pregnancy while in other studies the excretion of aldosterone glucuronide (27) and tet rahydroaldosterone (17) have been shown to in crease progressively upto the term which is in agreement with the findings of this study Previ ously it was shown that the overall metabolic clear ance rate of aldosterone is not greatly altered in pregnancy (30) The rise of urinary aldosterone ex cretion in this study from the 10th to 34th week of pregnancy is significant Thereafter the excretion decreases slightly until term and reaches the nonpregnant excretion level in 7 days after delivery

In general the rise of aldosterone secretion plays an important role in sodium balance during preg nancy The blood flow in the kidneys increases in early pregnancy (20) and the filtration of sodium increases in parallel If there were no antagonistic effect to the natriuresis the mother would lose all

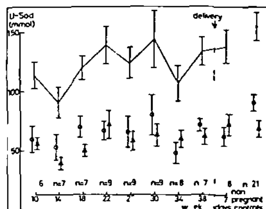


Fig 3 Mean levels (±S E M) of urinary sodium excre tion (U Sod) of 12 daytime hours (open circles) 12 night time hours (open triangles) and 24 hours (thick line) during pregnancy

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HYSTERECTOMY IN CENTRAL RECURRENCE OF CARCINOMA OF THE UTERINE CERVIX

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stract Central recurrence was recorded during 3–1972 in 136 patients (14%) out of a group of 977 cases en radiation therapy for carcinoma of the uterine cervix ages I and II) Fifty of these patients (i e 37%) showed ications for surgery In 12 of them only explorative arotomy was performed Radical hysterectomy was ried out in 14 cases combined vaginal and abdominal le extrafascial hysterectomy in 13 cases and ordinary rafascial hysterectomy was chosen in 11 cases e cellmorphology in the squamous-cell cancers clas ed according to Reagan et al was proportionally the ne in these patients as in the series as a whole The ients operated on by combined vaginal and abdominal sterectomy had the same rate of survival but fewer mplications than those given radical hysterectomy

ie favourable results from radiation therapy of rcinoma of the uterine cervix are well cumented (4 7 10 11 16) but in some patients e primary tumour does not respond and eventu y recurs Treatment of persistent viable cancer id recurrences has awakened much interest and fferent opinions have been presented as to how it iould be carried out (1 2 3 12 16 18)

This paper is an account of the results of hyster tomy in central treatment failures following radia on therapy of cancer of the uterine cervix in tages I and II

MATERIAL AND METHODS

he patient material consists of 977 cases of cancer of the terine cervix in Stages I and II recorded during 963–1972 (13) Radiation therapy was given using the tockholm technique which was successively modified fter 1969 to include high voltage treatment and fixed pplicator-combinations enabling the placement of a ell-defined known radiation dose in the tumour and in the true pelvis (11) During the same period of time an increasing number of adenocarcinomas were treated sur gically following preoperative radiation therapy

Information on the tumour situation in the patients who have died due to their cancer is lacking in two cases

Patients were considered to have central recurrence when after the conclusion of treatment tumorous growth was found in the uterus in the upper two-thirds of the vagina or in the proximal parts of the parametrium Spreading to other organs and metastases on the pelvic walls were not considered when defining central recur rence The patients have not been grouped according to progression of residual tumour or recurrence (5)

Central recurrence was recorded in 136 (14%) of the patients It was clinically and technically possible to perform surgery in 50 (37%) cases

The surgical procedure used during the first years was radical hysterectomy mainly using Okabayashi s method (14 patients) Eight of these patients were subjected to lymphadenectomy During recent years a more moderate form of hysterectomy has been carried out separating the uterine vessels medially to the ureters without dissecting the latter The operation is a combined vaginal and ab dominal procedure (9) and permits the removal of a well defined optional part of the vagina This technique was used in 13 patients Lymphadenectomy was not per formed

Ordinary abdominal extrafascial hysterectomy was done in eleven cases In four of these cases it was intended to perform radical hysterectomy but the presence of tumorous progression and/or pronounced postradiological fibrosis necessitated a more palliative therapeutic ap- proach

The tumour was so advanced in twelve patients that only exploratory laparotomy was performed

Results of surgery expressed in persistent or recurrent growth of tumour in the area subjected to surgery 2 and 5-year survival after operation for recurrence as well as fistulas between the urinary passages and the vagina and between the intestine and vagina have been recorded The microscopy of both the biopsy specimens and of the operative specimens was re-evaluated in those cases where hysterectomy was performed and the cell morphology was classified according to Reagan et al (15)

Table I *Microscopical findings in surgical specimens*

Type of operation	Vaginal resection not radical	Extensive tumour infiltration (>inner third of the cervix and/or tumour thrombosis)
Radical hysterectomy	1/14	9/14
Combined hysterectomy	1/13	10/13
Ordinary hysterectomy	5/11	5/11

RESULTS

Table I shows the results of the microscopical examination of the operative specimens in regard to the presence of tumour in the margins of the vaginal cuff infiltration in the cervix and tumorous growth in lymph or blood vessels

Colposcopy is now performed as clinical routine prior to combined hysterectomy but this was not done in case the vaginal resection was insufficient At combined hysterectomy >3/4 of the vagina was removed in three cases and in one case 1/2 to 2/3 of the vagina Colposcopy was not performed prior to the other hysterectomies

Table II shows continued tumour progression and/or central recurrence in the area of surgery (central parts of the pelvis) and recurrence adjudged to be limited to the upper part of the vagina

able III shows the cell picture according to
an et al among 36 patients who had hysterec
y and in 230 patients in Stages I and II during
0–1971 (8)

Attempts at curative treatment of recurrence following hysterectomy have only been made when the recurrence was limited to the upper part of the vagina In three cases resection of the vagina was done and in two cases fulguration These five patients are still alive One of them has in situ changes in the vaginal introitus The others are free from tumour

Complications from the urinary passages and the rectum are seen in Table IV

More than three fourths of the vagina was removed in the fistula patient who had combined hysterectomy

Repair of the fistula and re implantation of the ureters was performed in four of the fistula patients and in one of them ureteroileostomy was performed using Bricker's method One patient was operated on with ureterosigmoidostomy The recto-vaginal fistula was repaired These surgical measures were undertaken in the clinics of urology and surgery The two patients last referred to had recurrences and died within one year The others are still alive and free from tumour

None of the patients succumbed during the period immediately following surgery (within [illegible] months) Table V shows 2 and 5-year survival [illegible] operation for recurrence

DISCUSSION

The surgical methods used for treatment of central recurrence vary from exenterations of the true pelvis and radical hysterectomies to fulguration of the tumorous growth in the portio and in the vagina (1 2 3 12 16 18)

Radical hysterectomy according to Okabayashi's method was employed during the early years In troduction of high voltage therapy with relatively high absorbed radiation doses in the contents of the true pelvis caused pronounced fibrosis however This complicated or prevented the radical surgical approach which had been intended in some patients even when the spread of tumour was limited The frequency of complications increased and postoperative retroperitoneal fibrosis with compression of the ureters occurred in some patients in connection with vesico-vaginal fistulas

Conventional extrafascial hysterectomy gave satisfactory results except in those cases where the recurrence was diagnosed at a very early stage The difficulties in removing a sufficiently large part of the vagina in fibrous tissues make this surgical technique most often unsuitable as a curative treatment method

Table II *Recurrence in the operative area*

Type of operation	Central recurrence	Recurrence solely in the upper part of the vagina
Radical hysterectomy	5/14	–
Combined hysterectomy	5/13	3/13
Ordinary hysterectomy	5/11	4/11

le III *Distribution of patients according to*

	36 patients with hysterectomy for recurr 1963–1972	230 patients Stages I and II 1970–1971 (8)
-keratinizing ca	22 (~61 %)	170 (74 %)
atinizing ca.	5 (~14 %)	35 (15 %)
ll cell ca.	1 (~3 %)	6 (3 %)
noca and no-squamous ca	8 (~22 %)	19 (8 %)
al	36	230

Also it can be difficult to decide abdominally ere the vagina ought to be separated at radical sterectomy Combined vaginal and abdominal proach is a preferable alternative (9) We use poscopy for deciding where the vagina is to be ided and start the operation vaginally and there r usually do an abdominal extrafascial hysterec ny (type II hysterectomy according to Rutledge al (16) or wide extrafascial hysterectomy accord to Symmonds (18))

Adequate clearance of the vagina can be aranteed in this way The results have shown that s method gave adequate and free margins in all t one patient

The frequency of pronounced infiltration in the rvical wall and/or tumour thrombosis was about same for both the radical and the combined sterectomies

Recurrences were found in the area of surgery in central part of the pelvis during the postopera e period at the same rate in patients subjected to her radical or combined hysterectomy Recur nce in the upper part of the vagina alone was corded in three out of thirteen cases after com ned hysterectomy It was not possible to ascertain recurrence in the upper part of the vagina after dical hysterectomy due to necroses which often mained during a relatively long period of time llowing surgery

Recurrence in the vagina following hysterectomy an in many cases be treated successfully with local sections or fulguration

One patient among those treated by radical hys terectomy and one of those who received conven onal hysterectomy succumbed due to metastases n distant organs with no signs of tumour in the elvis after four years and one year respectively

The frequency of complications from the urinary tract and the intestine following radical hysterectomy was comparable to those found in the literature (16) but was lower in the patients treated by com bined hysterectomy This series of patients is how ever not large enough to permit any definite con clusions

The cytological details of squamous cell cancer as characterized by Reagan et al (15) have been used as a guide for a more individualized treatment (6 14 17 19) Johansson et al (8) were unable to show any obvious differences in tumour reaction to radiation therapy in a tumour material from 1969–1970 It was considered to be a representative sample out of the present tumour material from 1963–1972 The different cytological groups ought thus to be proportionally of the same size The distribution of the three different types of squamous cell cancers was the same in the patients treated by hysterectomy for central recurrence as in the whole material from 1969–1970 (Table III) There are however proportionally more patients among those treated by hysterectomy who have an adeno-squamous cancer or adenocarcinoma This agrees with the general opinion that adenocarcinoma has a poorer prognosis than squamous cell cancer

Three patients with non-keratinizing carcinoma in the biopsy specimens had keratinizing carcinoma in the operative specimens and one patient with keratinizing carcinoma primarily had non keratinizing carcinoma in the recurrent growth In two patients with adeno-squamous carcinoma the recurrent tumour showed only adenocarcinoma The microscopic morphology of the recurrent tumour thus coincides in most cases with that of the primary tumour

The prognosis following operation for recurrence varies greatly in part due to the selection which is

Table IV *Complications following operation for recurrence*

Type of operation	Vesico-vaginal fistula	Recto-vaginal fistula	Total
Radical hysterectomy	4/14	1/14	5/14
Combined hysterectomy	1/13	0/13	1/13
Ordinary hysterectomy	1/11	0/11	1/11

A IC

Table V *Two- and five year survival following operation for recurrence*

Type of operation	2 year survival	5-year survival
Radical hysterectomy	9/14	5/13
Combined hysterectomy	9/12	5/8
Ordinary hysterectomy	4/11	3/10
Total	22/37 (~60 %)	13/31 (~40 %)

made and in part dependent on the way in which radiation therapy is administered Barber (1966) reported 40% 5 year survival after radical hysterectomy and 19 7% following exenteration Calame (1969) reported that three out of seventy patients given primary radiation therapy in Stages I and II were still alive after 5 years or longer following operation for recurrence Rutledge (1976) got 55% 5 year survival for central recurrence treated with radical hysterectomy and 28% 5 year controlrate for those operated on by exenteration Kottmeier (1971) reported 41 9% 5 year survival following radical hysterectomy and 42 7% when only fulguration was given The present material is limited but the 5 year survival is close to that of the two series mentioned above

Barber (1971) indicates a 17 4% 5 year survival for pelvic exenteration in cases with non involved nodes and only 5 1% survival with lymph nodes involved He stated that it was concluded from this study that survival is poor the complications so h and in the vast majority the survival so brief difficult that pelvic exenteration is logically ntraindicated in the group of patients with involved nodes complicating the recurrence

The extremely poor prognosis when nodes are involved would indicate that routine lymphadenectomy is not justified at operation for recurrence In central recurrence the tumour is often limited to the cervix and the upper part of the vagina when the diagnosis is made (16) Spread to the lymph nodes probably implies that the tumour has developed into a systemic disease and that it is no longer curable with surgery

CONCLUSION

Even though the present series of patients is small it seems to support the assumption that central recurrence after radiation therapy for invasive cervical cancer in Stages I and II can be treated cally with combined vaginal and abdominal extrafascial hysterectomy without lymphadenectomy The same rate of 5 year survival is ach with fewer complications than have been rep for patients given radical hysterectomy

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WATER AND ION METABOLISM IN PLACENTA

I *Water and Ion Content of Rabbit Placenta in Different Periods of Gestation*

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tract Total tissue water of rabbit placenta decreases 18% between the 9th day and the end of gestation In same period intracellular water decreases by 40% and extracellular compartment swells Total tissue sodium chloride content increase by 34% and 27% respec ly from the 16th to the 33rd day while potassium de ases by 30% The intracellular concentration of these s does not vary greatly during gestation Moreover the il tissue magnesium content decreases by about 23% at end of gestation while its intracellular concentration s not show marked changes Calcium content of rabbit centa substantially increases during gestation and in ellular calcium shows a fivefold increase from the 16th the 33rd day of gestation The results are discussed in ms of relation between water and ion content and pla ntal tissue growth and aging

our programme of investigation of physiological d metabolic characteristics of placenta (11–14) we ve now undertaken a detailed study of water and n metabolism of rabbit placenta at different de ees of maturity The knowledge of the intimate echanisms that regulate intracellular water and n content would be of great interest in the com ehension of control systems which regulate the issage of many compounds across the placenta loreover a comprehensive set of information on us subject constitutes the basis for the study of athological conditions of this organ such as pla ntal insufficiency In addition the morphological atures of placenta (e g cytosyncytio-trophoblast) iake these studies particularly interesting since ey may reveal that basic physiological mech nisms such as regulation of cell volume and ion ontent and metabolism could be different from hose acting in other cells

We have been able to find only few often con tradictory data on this problem in the literature (3 5 9)

In this paper the first part of the work dealing with the water and mineral ion content of rabbit placenta in different periods of gestation is re ported

Rabbit placenta was chosen since it easily pro- vides a considerable amount of tissue at different ages of a reasonably short gestation Moreover it is possible to get placentae even 2 or 3 min after killing the animal a condition that is particularly useful since ion levels and equilibria are extremely sensi tive to cell energy metabolism and oxygen supply to the tissue

The results obtained show that in rabbit placenta from the 9th to the 33rd day of gestation (from the 31st to the 33rd day we deal of course with a post term gestation) total tissue water decreases by 18% intracellular water also decreases by about 40% while the extracellular space swells Total tis sue sodium increases and total potassium de creases K/Na ratio decreases gradually until it is reversed while the intracellular concentration of both ions does not vary significantly The most impressive change is however related to calcium Both total tissue and intracellular calcium show a marked increase during placental growth and senescence Total magnesium content declines at the end of gestation whilst its intracellular concen tration is kept constant

The results will be discussed in terms of placental tissue aging

Table I *Ion content of rabbit placenta at different periods of gestation*

Period of gestation (days)	Ion content (mmoles/kg d wt)						
	Sodium	Chloride	Potassium	Magnesium	Calcium	Na/Cl	K/Cl
I (9–15)	498 2±26 (45)	407 4±23 (45)	566 7±19 (44)	44 6±2 (42)	82 8±9 (39)	1 2	1 1
II (16–20)	375 2±16 (32)	310 2±7 (32)	521 8±11 (32)	44 3±2 (31)	61 5±6 (27)	1 [illegible]	[illegible]
III (21–25)	433 4±11 (20)	318 4±17 (17)	447 0±10 (20)	43 7±1 (15)	85 5±7 (16)	1 3	[illegible]
IV (26–30)	497 3±17 (15)	350 8±10 (14)	431 1±12 (15)	35 7±8 (14)	123 6±19 (14)	1 4	[illegible]
V (31–33)*	504 0±13 (24)	394 3±17 (23)	367 5±13 (23)	33 2±1 (24)	155 0±11 (24)	1 2	0 7

Mean±S E of the mean (no of observations)
* Pregnancy has been prolonged beyond term (V period) by daily treatment with s c injection of 1000 I U chorionic gonadotrophin (HCG) from the 27th to the 32nd day of gestation

MATERIALS AND METHODS

Pregnant white giant New Zealand rabbits at known days of gestation were kept on standard diet Some animals were brought beyond the physiological term of their gestation (30 days) by a daily s c injection of 1000 I U of human chorionic gonadotrophin (HCG) starting from the 27th day of their gestation The study was carried out on placentae obtained from the 9th to the 33rd day of gestation This interval has been arbitrarily subdivided into five periods as follows period I from the 9th to the 15th day of gestation period II from the 16th to the 20th period III from the 21st to the 25th period IV from the 26th to the 30th period V from the 31st to the 33rd Pregnancy was not further prolonged since about half of the fetuses were already found dead at the 33rd day Furthermore placentae of this last period showed extensive areas of necrosis and infarction

Rabbits previously injected i v with 5000 I U heparin (1 ml Liquemin-Roche) were killed by cervical dislocation and bled by carotid incision The blood was collected for ion determination After bleeding the abdomen was open and the pregnant uterus withdrawn Placentae were care and quickly dissected from endometrium and s and care was taken to discard necrotic areas es were taken by cutting small pieces of tissue of ut 100–150 mg which were gently blotted on hardened lter paper (Whatman no 54) and placed in tared screw cap plastic bottles The bottles were weighed in order to determine the wet weight (w wt) and then dried overnight in an oven at 80°C The day after the bottles were weighed again after a period of equilibration at room temperature in a dessicator to determine the dry weight (d wt) and calculate the amount of tissue water expressed as kg/kg d wt

For the analysis of ion content the tissue was extracted by 0 1 N HNO_3 for at least four hours at room temperature since this procedure has been shown to extract quantitatively all ions from many tissues (7) Ions were determined on the acid extract by atomic absorption spectrophotometry For sodium and potassium a final concentration of 0 06% of CsCl was added to standards and samples while for calcium and magnesium 1% $LaCl_3$ was added Chloride content was determined spectrophotometrically at 460 nm following Zall et al (24) Deionized water (Milli Q Reagent Water System Millipore Corporation Bedford Mass USA) was used throughout the experiments αCl (fraction of tissue water chloride at the same concentration of plasma calculated on the basis of plasma chloride concentr of 111 7±1 7 corrected by the Donnan factor for chl of 0 977 (8 15) Tissue water extracellular (H_2O_e) intracellular (H_2O_i) compartments were calculated the expression $H_2O_e = H_2O_{tot} \times \alpha Cl$ and H_2O_i H_2O $(1-\alpha Cl)$ Intracellular ion concentration was calc by subtracting the amount of ion dissolved in the ex cellular water at the same concentration as in the pl from the total issue ion content and dividing this value the intracellular water

RESULTS

Table I summarizes the ion composition of ra placenta at different ages of gestation Sodium c tent decreases by 25% in period II of gestation increases progressively by about 15% from pe II to III and III to IV in which the content stab around 500 mmoles/kg d wt through period V differences among the first four periods are sta cally highly significant ($p<0\ 0005$) The behav of chloride strictly follows that of sodium d creases by 25% in period II and it increases f 310 2±7 to 394 3±17 mmoles/kg d wt Na/Cl is kept constant at a value of 1 2–1 4 The conc potassium decreases gradually from 566 7±1 367 5±13 mmoles/kg d wt (35%) at a probab level of 99 95% between each pair of periods K ratio shows a progressive lowering from 1 4 (pe II) to 0 7 (period V) The content of divalent cat markedly changes during placental growth In calcium although decreasing by 35% in perio undergoes a substantial increase ($p<0\ 0005$) in subsequent period and reaches a level of 155 0 mmoles/kg d wt in period V Magnesium decre by 20% in periods IV and V

The amount of total tissue water (H_2O_{tot}) is ported in Table II It decreases from the first to

Tissue water Chloride apparent concentration in tissue water Fraction of tissue water contain at the same concentration of plasma water (αCl) and extracellular and intracellular water ments of rabbit placenta at different periods of gestation

H_2O_{tot} (kg/kg d wt)	$[Cl^-]$ tissue water[a] (mmoles/kg tissue H O)	αCl[b]	H_2O (kg/kg d wt)	H_2O_i[d] (kg/kg d wt)
6 2± 3 (44)	65 7±6 8[f]	575± 068[f]	3 6	2 6
5 5± 06 (31)	56 4±1 9	493± 0?4	2 7	2 8
5 2± 09 (17)	61 2±4 3	535± 045	2 8	2 4
5 4± 07 (14)	65 0±2 7	578± 063	3 1	2 3
5 1± 1 (?4)	77 3±4 9	676± 053	3 4	1 7

ted on the basis of mean slices chloride content of Table I and mean total tissue water of this Table
nt Cl in tissue water/(concentration in plasma water)×(Donnan ratio) The Donnan factor for Chloride (0 977)
s the ratio of Cl^- distribution between plasma and tissue interstitial fluid (8 15) Plasma Cl =111 7±1 7 (16)
g plasma water
extracellular water=tissue $H_2O \times \alpha_{Cl}$
ntracellular water=tissue $H_2O \times (1-\alpha_{Cl})$
S E (no of observations)
lculated as error propagation from the original data Cl plasma total tissue H O Cl content of tissue

od The difference is highly ignificant 05) On the basis of the above reported ments we have calculated extracellular and ular water compartments This determina sually done by the use of extracellular space such as inulin polyglucose and others ch markers require at least one to two hours ation in order to obtain a satisfactory equi of the marker substance while all our tests en performed a few minutes after withdraw placenta Therefore following other au e water compartments were determined on s of tissue chloride content assuming that ide is confined to the extracellular space

The data obtained by following the latter assumption can give overestimated values since cellular membranes are not impermeable to chloride the predominantly extracellular distribution of this an ion being determined mainly by a membrane potential negative at the interior (2 6) Once membrane potentials directly measured by electrophysiological methods are known it is easy to derive an expression to correct for intracellular chloride (15) We were not able to bring such correction to our calculation since we have not found any published values of placental cell membrane potential αCl determined in placentae at different periods of gestation are reported in Table II together with

l *Calculated intracellular concentrations of sodium potassium calcium magnesium and calcu for sodium and potassium of rabbit placenta at different periods of gestation*

r	Intracellular concentration (mmoles/kg intracellular water)					
	Sodium	Potassium	Calcium	Magnesium	Em [a] (mV)	Em [a] (mV)
5)	−4 2	207 5	23 6	15 6	–	−90 4
0)	−4 5	181 9	16 4	15 0	–	−94 0
5)	14 7	178 7	28 7	17 0	6? 7	−94 5
0)	25 2	177 7	45 4	14 0	47 9	−94 7
3)	6 8	211 1	81 8	18 1	84 0	−89 9
	14? 9±1 9 (1?)	5 5±0 3 (16)	5 8±0 2 (?8)	0 96±0 03 (?5)		

llular concentrations have been cal-ulated on the basis of mean water and ion content of Tables I and III and n concentrations of this Table
rane potential for Na and K $= \frac{RT}{F} \times \log \frac{[Na\ ]i}{[Na\ ]}$ or $\log \frac{[K\ ]e}{[K\ ]}$
s/kg plasma water (Plasma H_2O=931±1 4 kg/kg plasma)

Cl^- in total tissue water and with the calculated size of both extracellular and intracellular compartments From periods II to V αCl gradually increases up to a maximum of 0 676±0 053 The amount of extracellular water accordingly increases from 2 7 to 3 4 kg/kg d wt (+26%) despite the lowering of total tissue water On the contrary the intracellular water decreases gradually from periods II to V by 40%

Data of Table III were calculated on the basis of the above reported water and ion values The intracellular concentration of each ion was calculated from the size of intracellular compartment (Table II) and plasma ion concentration (last row of Table III) Furthermore in the two last lines membrane potentials for Na^+ and K^+ calculated from the Nernst equation are also reported Intracellular concentrations of potassium and magnesium do not vary greatly during the course of pregnancy while $[Na^+]_i$ increases from the values that approach 0 in the first two periods to the higher levels found subsequently However the most striking changes concern $[Ca^{2+}]_i$ The apparent concentration of this cation increases progressively from 16 4 (period II) to 81 8 mM (period V) The calculated membrane potential for K^+ (Em_K+) indicates that no substantial variation of this parameter takes place during placental growth and senescence Cell membrane potentials for Na^+ show the expected changes due to the different intracellular sodium found in the different periods

DISCUSSION

Tissue water

The results reported show that physiological growth of rabbit placenta is characterized by a decrease and redistribution of total tissue water The older the tissue becomes the more its water content decreases down to a drastic decrease in the senescent placenta of the past term pregnancy An interesting feature is that the loss of water is accompanied by an expansion of the extracellular compartment as documented by the increase of αCl that starts from the period II This can be explained by the more abundant collagen synthesis that takes place during growth in the villous axis Furthermore the decrease of total tissue water appears to be the sum of a substantial decrease of the intracellular compartment (about 40%) and a smaller increase (25%) of the extracellular fraction

Our results can be interpreted as an exp[illegible] placental involution and senescence a[illegible] the well known relation between tissue wa[illegible] and aging

Ion content

In this work we took into consideration the [illegible] which are more evidently linked to [illegible] perties of mammalian cells The ma[illegible] sodium and potassium gradients is in fact [illegible] energy dependent property of li[illegible] Moreover calcium and magnesium in[illegible] concentrations are always more evident[illegible] lated to regulation of cellular metabolism.

From data of Table I it appears that plac[illegible] is strictly correlated to the total tissue ion [illegible] although with some differences among the [illegible] ions Sodium increases significantly and pr[illegible] sively from period II to the end of [illegible] whereas potassium decreases The possibil[illegible] these changes can be due to tissue blood [illegible] more abundant toward the end of gestation [illegible] out if one considers that they are inconsist[illegible] an increase of red blood cells which are ve[illegible] potassium On the contrary we could [illegible] that the increase of erythrocytes induces a[illegible] estimation of the changes observed (pot[illegible] could be much lower in older place[illegible] cellular concentration of potassium does n[illegible] greatly as shown also by calculated Em[illegible] latter values in default of directly measured [illegible] tials are the only available for these cells [illegible] fall perfectly in the range of potentials meas[illegible] other cells (e g muscle cells) Intracellular [illegible] tration of sodium behaves in a different wa[illegible] period II its concentration is about zero a[illegible] comes higher in period V Sodium is usuall[illegible] outside the cell by an active pump (the [illegible] stimulated ATPase) This is also probably the [illegible] in placental cells which extrude sodium ag[illegible] gradient sustained by the plasma concentra[illegible] about 140 mM The increase of intracellular so[illegible] concentration may indicate that the efficiency [illegible] extruding pump is failing and this would be [illegible] tent with a documented decrease of the ener[illegible] duction system in ageing placentae (11 1[illegible] tissue magnesium has a break point between the [illegible] and the following periods but as far as its in[illegible] lular concentration is concerned it remai[illegible] changed at a level of about 16 mM The co[illegible] ous imbalance of the intracellular magnesium [illegible]

versus plasma concentration (0 96 mM) ıat as ın other mammalian cell systems (8) s possibly concentrated ın the cell ınterior may be prevalently bound to subcellular s (18) Calcium behaves differently ın as compared to other tissues This cation lered an extracellular constituent (8) being ıde by energy dependent mechanisms (10 or hetero-exchange diffusion processes (1 our determinations the level of both total nd intracellular Ca^{2+} are much higher than ma values It is widely acknowledged that is easily bound to necrotic tissue areas In of the placenta this can be true ın the two ıods studied but is extremely unlikely to be lanation in the preceding periods in which e is completely free of necrosis and infarc However the possibility of microfoci of still remains With regard to the high content of this organ the peculiar role he placenta plays ın the transfer of calcium aternal serum to fetus must be taken into ration Calcium is actively transported placental cells (4 23) and this hypothesis is ed by the evidence of a Ca^{2+}-dependent e in plasma membranes of this organ (20 21

results at the placental ages grouped ın the I require an additional discussion In this ın fact some of the parameters we have (i e total tissue sodium and chloride total ı and intra-extracellular water compart do not fit with the sequentiality that comes m the data analysis of the following groups ınt first of all to underline the technical ties related to the study of placentae at the etween 9 and 15 days The exiguity of ta renders unavoidable contamination by urrounding tissues such as endometrium mbranes Moreover we could speculate that served differences are linked to the peculiar ical conditions of placenta ın the first half of on when cell growth prevails over tissue in ph and senescence

results of the study we have undertaken on content and ionic composition of rabbit ıta in different periods of gestation lead to the ıng conclusions placental growth and cence are characterized by a decrease of total water content accompanied by both the age of the intracellular water compartment and the swelling of the extracellular compartment As far as the monovalent cation content (Na^+ and K^+) is concerned we can say that only sodium shows a clear increase throughout the placental growth while potassium content reflects the changes in size of extracellular and intracellular water compartments Magnesium undergoes a clear decrease toward the end of pregnancy while calcium shows a fivefold increase from the 16th to the 33rd day of gestation

Further studies are ın progress with the aim of understanding the observed changes from a func tional and metabolic point of view

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SHORT COMMUNICATIONS

EARLY PRENATAL CHROMOSOME ANALYSIS OF 604 FETUSES

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l chromosome analysis may now be considered itine which should be offered to women at risk iving children with chromosomal diseases Few series are available Large series are neces for the evaluation for example of the cost tiveness of the procedure Therefore the re ı of fetal chromosome analysis in 604 unselected nts are presented The value for the individual nt is already obvious Further details will be lished later

MATERIAL AND METHODS

n March 1973 to February 1976 chromosome analysis offered to all pregnant women referred to our hospital isk having a chromosomally abnormal child Furthermore chromosome analysis was carried out when amniocentesis was done for other purposes in the second trimester e g for alpha feto-protein-determination in women at risk of having neural tube defects In a number of cases women came to the hospital with the expressed wish of having a fetal chromosome investigation done for a number of other reasons The test was carried out whenever possible Only very few of those offered the analysis refused to have it and there was no reason to believe that these had a different risk from those having the investigation

Amniocentesis was carried out around the 14th–15th week sometimes later Ultrasound was used in all cases (?) Amniotic cell cultures were carried according to methods earlier published (15) Results were obtained in all cases

In three cases twins were diagnosed by ultrasound and amniotic fluid obtained from both fetuses In three cases twins were present but not diagnosed

ıle 1 *Elevated risk of chromosome abnormality*

	No investigated	No abnormalities		%
ılial translocations	3	0 (3)		–
nked disease	15	(8 males)		53
ther has chromosome abnormality	3	0		–
ther 40 years or more	133	5 1 47,XY +13 1 47,XX +18 2 47,XX +21 1 47,XY +21 (1 46,XX ?p+ 6p−)	3 7	1 7
ther 35–39 years	208	1 1 47,XX +21 (1 46,XX t (17/22))	0 4	
ıther earlier born child ıth chromosome abnormality	37	0		–
	399	6 (14)		1.5 (3 5)

Table II *X linked diseases (8 male fetuses 5 abortions*

No abortion in 3 cases

1 Haemophilia diagnosis not confirmed when patient admitted for abortion from other hospital
2 Patient had 2 male children with congenital malformations of sex organes Did not want abortion Had malformed male child
3 Father had haemophilia Parents wanted only boys

Table III *Normal' risk of chromosome abnormality*

	No investigated	No abnormalities	%
Previous child with congenital malformations inborn errors of metabolism oligophrenia or other diseases	37	0	–
Previous child with spina bifida anencephaly hydrocephaly	44	1 (47,XYY)	2 2
Mother has spina bifida/hydrocephaly	2	0	–
Down s syndrome in the family	49	1 (47,XXX)	2 0
Patients wish investigation	34	0 (45,XX t) (14/22)	–
Other	39	0	–
	205	2	0 9

A total of 604 fetuses from 601 pregnant women were examined The patients were divided in two groups group e having a *higher than normal* and group two a not er than normal risk of having a child with a chromoe abnormality

Table IV *References cited*

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Gerbie et al , 1971 (includes figures from Nadler 1970)
Hsu et al 1973
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Doran et al 1974
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Lindsten et al 1974
Milunski et al 1974
Nier Meyer 1975
Philip et al 1974
Laurence & Gregory 1976

Group 1 Elevated risk of chromosome abnormality

Table I shows that 6 chromosome abnormalities [illegible] balanced translocations) were found among 399 [illegible] (1.5%) In 8 of 15 cases with a risk of X linked disease male fetus was ascertained 14 (3 5%) had thus an indication for abortion but only 11 abortions were carried [illegible] (*Table II*)

Group 2 Normal' risk of chromosome abnormality

Table III shows that two chromosome abnormalities [illegible] one balanced translocation (not familial) was found [illegible] abortions (0 9%) were carried out

DISCUSSION

The numbers in each of the groups are small This also true for those results available in the literature (Table IV) By evaluation of the results from the literature and those from an unpublished large series from Germany and the collected results [illegible]

Table V

	Literature survey			German survey			European survey		
	No invest	No abnorm	%	No invest	No abnorm	%	No invest	No abnorm	[illegible]
Familial translocations	91	13	14	36	4	11	179	[illegible]	[illegible]
X linked diseases	149	75	50	16	7	43	280	[illegible]	[illegible]
High maternal age	1 404	41	2 8	728	22	3 6	1 293 (2 269)[b]	63	[illegible]
Earlier chromosome abnormality	630	11	1 7	295	6	2 9	1 047	14	[illegible]
Other indications	776	12	1 5	193	(1)	(0 5)			

[a] 35 or 40
[b] Age information only available for 1 293

on of risks based on available

tr ns	4–14%
l dis	43–53%
s age ears	1 7–3 7%
currence risk	(0–) 1 7–2 7%

opean Centers (Galjard in press) (Table V) : figures for risks are obtained (Table VI) figures may be representative and may be the analysis of cost effectiveness This is to be of importance at the present time in Western countries where research funds for romosome analysis are no longer available

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XLINKED VALUES OF E ROSETTE FORMING LYMPHOCYTES IN MOTHER AND NEWBORN

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The T-cell marker of spontaneous rosettes with erythrocytes was determined in 34 normal term-s on the peripheral lymphocytes of the mother corresponding cord-blood lymphocytes of the n immediately after delivery A consistently lower E-rosette forming lymphocytes was observed in compared to female newborns in different parity and in twin deliveries. When the mean values were ed for corresponding E-rosettes of maternal and n lymphocytes in each group (female and male of offsprings) they were nearly identical

-cell marker of spontaneous rosettes with erythrocytes has been studied by various in ators in the cord blood of healthy infants and values ranging from 35-53% are reported (2 In a previous study we reported some obser is concerning the possibility of a balanced re ship between maternal and newborn E rosette ng lymphocytes (4)

o groups of maternal newborn pairs were d in one group the percent of F-rosette form ymphocytes was high in the mother and low in newborn (58% and 36%) while the opposite ionship was obtained in the second group (43% 37%) At the same time the mean values of osette forming cells in each group was similar % and 41% respectively)

he aim of the present investigation was to find if this feto-maternal relationship could be corre ed with parity or with the sex of the newborn

PATIENTS AND METHODS

Following essentially the method of Bentwich et al. (1) ontaneous rosettes with sheep erythrocytes were de rmined on the peripheral lymphocytes of the mother and e corresponding cord blood lymphocytes of the newborn immediately after delivery in 34 normal term-deliveries (Of the 34 mothers studied 11 were after their first deliv ery 10 after the second 9 after third or subsequent and 4 after twin deliveries) (dizygotic twins 3 cases with male-female offsprings and one case with two male offsprings)

E rosettes in twins were determined separately from each placenta For the calculation of the mean percentage of E rosette forming T-cells 300 lymphocytes were counted for each mother and corresponding newborn

RESULTS

A consistently lower level of E rosette forming lymphocytes was observed in male newborns (34–45% mean 37%) as compared to female newborns (42–55% mean 44%) in all parity groups including twin deliveries

In contrast to all other groups the mean percentage of E rosette forming cells in twin de liveries (male and female offspring) was higher in the newborn than in the mother In all 4 cases of twin deliveries the mean value of E rosette forming cells of the mother was below 50% and lower as for the other groups (see Table I)

The mean values of maternal and newborn E rosette forming lymphocytes for each group (females and males) were nearly identical 47% and 44% respectively Similar mean values were ob tained in our previous experiment (4)

DISCUSSION

The existence of a consistently lower percentage of E-rosette forming lymphocytes in male compared to female newborns suggests a possible role for sex linked histocompatibility antigens in the feto-maternal relationship (5 6) A decreased T

11 keto etiocholanolone	<0 91 μmol
11 hydroxy androsterone	2 2 μmol
11 hydroxy-etiocholanolone	0 51 μmol
A/E ratio	0 86
11 ratio	8 0

SURGICAL OBSERVATIONS

13 5 l of yellow brown opaque fluid were withdrawn by abdominal puncture The fluid was aseptic free from cellular elements and composed of protein colloidal particles Laparotomy revealed a large flabby thick walled cyst attached by a suspensory ligament to the right side On the left side a 4×2 5×2 cm whitish formation also attached by a suspensory ligament was found Neither uterus nor uterine tubes were present Small grain seed like objects were found in the pouch of Douglas and up along both sides samples of which were taken for biopsy The removed cyst weighed 2950 g and contained a pale fluid An object which was firm and the size of a small hen s egg was found embedded in the cyst wall

The following patho-anatomical description was given (Dr Love Jepsen) The cyst s wall was composed of a thick layer of collagen connective tissue The luminal side was lined by a single layer of epithelium composed of low cylindrical to cubical cells the nuclei of which were round and regular Small papilliform structures as well as small psamoma like bodies were scattered in the luminal layer Below the epithelium a thin layer of macrophages was found Histological diagnosis Mesothe [illegible] cyst

[illegible] peritoneal biopsy showed adipose and con [illegible] tissue enclosed cysts The lining of these cysts was a mesothelial like epithelium within which were scattered small psamoma like structures Neither epitheloid granuloma nor malignant changes were found Histological diagnosis Mesothelial cyst Both gonads were testicular structures corresponding to testicular feminizing of complete type

DISCUSSION

Heidenreich in 1975 (2) described a pa [illegible] ing from t f whose right gonad lay emb dde [illegible] wall of a child s head sized cyst The cyst [illegible] was composed of collagen connective tissue [illegible] an outer coat of smooth muscle cells and a lume lined with a single layer of cubical and cylindrical cells The patient s vagina was about one finger [illegible] length Heidenreich proposed that the cyst had developed from the Mullerian tubular system and suggested that it resulted from failure of tes [illegible] inhibition (Oviduct repressor Mullerian [illegible] hibiting substance) of the development of [illegible] Mullerian system

Several similarities between the case repo [illegible] this paper and that described by Heidenre [illegible] seen but since no rudimentary remnants [illegible] Mullerian tubular system were found we are no [illegible] able to support the hypothesis proposed b [illegible] Heidenreich

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WHO RECOMMENDED DEFINITIONS TERMINOLOGY AND FORMAT FOR STATISTICAL TABLES RELATED TO THE PERINATAL PERIOD AND USE OF A NEW CERTIFICATE FOR CAUSE OF PERINATAL DEATHS

Modifications Recommended by FIGO as Amended October 14 1976

The following limits for the inclusion ...irths and perinatal death in statistics ... recommended

... That all fetuses and infants delivered weighing ...g or more be reported in the country s statistics ...ther or not they are alive or dead It is rec...ized that legal requirements in many countries ... set different criteria for registration purposes ... is hoped that the countries will arrange the ...stration or reporting procedures in such a way ... the events required for inclusion in the statis... can be identified easily (WHO—Approved by ...IO)

... That mortality statistics reported for purposes ...international comparison should include only ...se born weighing 1000 g or more (WHO—...proved by FIGO)

Perinatal Statistics

... *Birth Weight*

...e first weight of the fetus or newborn obtained ...er birth This weight should be measured prefer...y within one hour of life before significant post...tal weight loss has occurred (WHO—Approved ... FIGO)

... *Low Birthweight*

...ss than 2500 g (WHO—Modified by FIGO by ...leting the words up to and including 2499 g)

...3 *Gestational Age*

...e duration of gestation as measured from the first ...y of the last normal menstrual period Gestational ...e is expressed in completed days or completed weeks (e g events occurring 280 *to less than 287 days* after the onset of the last normal menstrual period are considered to have occurred at 40 weeks of gestation)

Measurements of fetal growth as they represent continuous variables are expressed in relation to a specific week of gestation (e g the mean birth weight for 40 weeks is the one obtained at 280 *days —less than 287 days* of gestation on a weight for gestational age curve) (WHO—Accepted by FIGO)

2 4 *Perinatal Period*

The perinatal period is the one extending from the gestational age at which the fetus attains the weight of 1000 g (equivalent to 28 *completed* weeks of gestation) to the end of the seventh completed day (168 *completed* hours) of life (WHO—Approved by FIGO is the word *completed* is included where underscored)

2 5 *Pre Term*

Less than 37 completed weeks (less than 259 completed days) (WHO—Accepted by FIGO)

2 6 *Term*

From 37 completed weeks to less than 42 completed weeks (259 to 293 days) (WHO—Accepted by FIGO)

2 7 *Post Term*

Forty two completed weeks or more (WHO—Approved by FIGO)

2 8 *Birth*

Complete expulsion or extraction from its mother of a fetus irrespective of whether or not the umbili

11 keto etiocholanolone	<0 91 μmol
11 hydroxy androsterone	2 2 μmol
11 hydroxy-etiocholanolone	0 51 μmol
A/E ratio	0 86
11 ratio	8 0

SURGICAL OBSERVATIONS

13 5 l of yellow brown opaque fluid were withdrawn by abdominal puncture The fluid was aseptic free from cellular elements and composed of protein colloidal particles Laparotomy revealed a large flabby thick walled cyst attached by a suspensory ligament to the right side On the left side a 4×2 5×2 cm whitish formation also attached by a suspensory ligament was found Neither uterus nor uterine tubes were present Small grain seed like objects were found in the pouch of Douglas and up along both sides samples of which were taken for biopsy The removed cyst weighed 2 950 g and contained a pale fluid An object which was firm and the size of a small hen s egg was found embedded in the cyst wall

The following patho-anatomical description was given (Dr Løve Jepsen) The cyst s wall was composed of a thick layer of collagen connective tissue The luminal side was lined by a single layer of epithelium composed of low cylindrical to cubical cells the nuclei of which were round and regular Small papilliform structures as well as small psamoma like bodies were scattered in the luminal layer Below the epithelium a thin layer of macrophages was found Histological diagnosis Mesothe l cyst

e peritoneal biopsy showed adipose and con tive tissue enclosed cysts The lining of these cysts was a mesothelial like epithelium within which were scattered small psamoma like structures Neither epitheloid granuloma nor malignant changes were found Histological diagnosis Mesothelial cyst Both gonads were testicular structures corresponding to testicular feminizing of complete type

DISCUSSION

Heidenreich in 1975 (2) described pa [illegible] ing from t f whose right gonad lay emb dde [illegible] wall of a child s head sized cyst The cyst [illegible] was composed of collagen connective tissue [illegible] an outer coat of smooth muscle cells and a [illegible] lined with a single layer of cubical and cylind[illegible] cells The patient s vagina was about one finger [illegible] length Heidenreich proposed that the cyst had de veloped from the Mullerian tubular system [illegible] suggested that it resulted from failure of testi[illegible] inhibition (Oviduct repressor Mullen[illegible] hibiting substance) of the development of the Mullerian system

Several similarities between the case report[illegible] this paper and that described by Heidenreich can [illegible] seen but since no rudimentary remnants of the Mullerian tubular system were found we are [illegible] able to support the hypothesis proposed [illegible] Heidenreich

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v Neonatal Mortality Rate

$$\frac{\text{eonatal deaths of infants 1000 g and over at birth}}{\text{rn infant weighing 1000 g er}} \times 1000$$

—Approved by FIGO)

tillbirth Rate

$$\frac{\text{rn infants weighing 1000 g er}}{\text{rn infants weighing 1000 g er+live born infants weighing and over at birth}} \times 1000$$

—Approved by FIGO with the suggested cation of adding the italicized words *at*)

Recommendations for Further Analysis

iore detailed analysis of data on the perinatal l concerned with birthweight and gestational tatistics should be presented in a uniform way i allows comparisons to be made easily

tailed tables should be given where appro- related to the total number of infants identifying separately those stillborn those orn but dying in the first 7 days and those ving 7 days

By Birthweight

weight interval of 500 g is accepted by FIGO iot the method of designation i e 1000–1499 g -1999 g etc Because some confusion might ir for an infant weighing 1499 5 g FIGO prefers ollowing techniques of designation From 1000 less than 1500 g to less than 2000 g and so on

By Gestational Age[1]

weekly intervals are accepted by FIGO but not technique of designation because it is felt that e is some margin for error Because a weekly rval does not gain a numerical designation until 7 days of that interval have been completed i e k no 1 is so designated when the first 7 days have been completed the 2nd week when 14 days have been completed and so on FIGO suggests the following technique for designating weekly intervals

Gestational Age

28 weeks to less than 32 completed weeks (196 days to less than 224 completed days)

32 weeks to less than 36 completed weeks (224 days to less than 252 completed days)

36 weeks to less than 38 completed weeks (252 days to less than 266 completed days)

38 weeks to less than 42 completed weeks (266 days to less than 294 completed days)

42 completed weeks (294 days) and over

5 3 For early neonatal deaths by age of death using the following intervals

Birth to less than 60 completed minutes
1 hour to less than 12 completed hours
12 hours to less than 24 completed hours
24 hours to less than 48 completed hours
48 hours to less than 72 completed hours
72 hours to less than 168 completed hours

Where detailed information is not available data on age at death should be provided as follows

Birth to less than 60 completed minutes
1–less than 24 completed hours
24–less than 168 completed hours
(WHO—Modified by FIGO)

In each table appropriate totals and subtotals should be given (for example all infants with birth weight *1000 up to less than 1500 g* or all infants of 28 to *less than 38 completed* weeks gestation etc (together with appropriate percentages If more detailed breakdowns are tabulated it should be possible to aggregate them into the above groupings (WHO—Approved by FIGO with the italicized suggested modifications)

6 0 Mortality Statistics

These should be presented in relation to different groups of infants using the definitions of rates given below

6 1 *Stillbirth and Perinatal Death Rates*

(*a*) all infants 1000 g or more
(*b*) all infants 1000 g or more in 500 g groups

[1] e duration of gestation is measured from the first day he last normal menstrual period Gestational age is essed in completed days or completed weeks (e g its occurring 280 to less than 287 days after the onset ie last menstrual period are considered to occur at 40 ks of gestation)

11 3 While the supplementary information to be collected at death or stillbirth may be varied in accordance with the wishes of the individual countries it is recommended that consideration be given to the collection of the following items as a minimum

Mother

Date of birth

Previous history

Number of previous pregnancies live births/stillbirths/abortions

Outcome of previous pregnancies live births/stillbirths/abortions and date

(WHO—Approved by FIGO)

GYNECOLOGIC TERMS AND DEFINITIONS

2 1 *Postmenstrual phase (Menstrual period Menstruation Menses)*

The postmenstrual phase is the phase that includes the 4–5 days following the menstrual phase The endometrium is thin measuring ordinarily only 1 or 2 mm in thickness The surface epithelium and the epithelium lining the glands is of cuboidal type The endometrial glands are straight narrow and collapsed the stroma is dense and compact

2 2 *Proliferative Phase*

The proliferative phase is the growth phase of the endometrium The endometrium is stimulated by estrogen The endometrial glands are straight and short and the glandular epithelium is cuboidal and hows no evidence of secretory activity The al cells multiply and the spiral arteries begin to grow

2 3 *Secretory Phase*

The secretory phase is the postovulatory phase of the endometrium The endometrium is stimulated by estrogen and progesterone The endometrial glands are long and tortuous The glandular epithelium is columnar and filled with secretion The stromal cells are large and the spiral arteries are long and tortuous

2 4 *Premenstrual Phase*

The premenstrual phase is the phase that includes the 2–3 days prior to the menstrual phase and corresponds to the regression of the corpus luteum The chief histologic char en infiltration of the stroma po mononuclear leukocytes pro flammatory appearance (oncu framework of the strom in disintegrates As a result of the and secretion the thickness o often decreases significantly du g t d fore the menstrual phase In the pro d tion the glands and arteries collapse

2 5 *Menstrual Phase—Menstrual Period*

The menstrual phase is the period of of the endometrium There are of polymorphonuclear leukocytes plasm and other wandering blood cells in the tissue

2 6 *Amenorrhea*

Amenorrhea is the absence of menstruation It be primary or secondary physiologic or path It is a subjective but not a reliable sign of p nancy

2 7 *Amenorrhea Pathologic*

Pathologic amenorrhea is the cessation of men ation for at least 3 months at any time after pub other than during pregnancy and lactation fore the onset of menopause It can be either p mary or secondary and caused by any of the fol ing factors congenital abnormalities central ne ous system lesions systemic conditions disturbances and uterine trauma

2 8 *Amenorrhea Physiologic*

Physiologic amenorrhea is the normal abs menstruation before the menarche during p nancy and lactation and after the menopause

2 9 *Anovular Menstruation (Anovular Bleeding)*

Anovular menstruation is menstrual bleeding out discharge of an ovum

2 10 *Dysmenorrhea*

Dysmenorrhea is a symptom characterized by p ful menstruation

2 11 *Mechanical Dysmenorrhea*

Mechanical dysmenorrhea is a menstrual pa to cervical stenosis or other obstruction to strual flow

inctional Dysmenorrhea

hea menstrual pain observed
ly nc worthy pelvic lesion

Acqi red Dysmenorrhea

orrhea is menstrual pain caused
en lvic disease

Hyp norrhea

enorrhea is a diminution in the amount of
or a shortening of the duration of menstrua

Mittelschmerz

chmerz is intermenstrual pain in the lower
n generally associated with ovulation

Oligomenorrhea

enorrhea is a reduction in the frequency of
lation An interval between the cycles of
than 38 days but less than 3 months indi
igomenorrhea

Puberty

is the period when a person becomes sexu
ture The reproductive organs become func
and secondary sex characteristics are de
l

icarious Menstruation

us menstruation is bleeding from any
other than the mucous membrane of the
cavity It occurs periodically at the time
ormal menstruation should take place

Abruptio Placentae

io placentae is the complete or partial de
nt of the normally implanted placenta from
rine wall at 20 weeks or more of gestation
io placentae may occur in conjunction with
a previa Hypofibrinogenemia is the most
n complication of abruptio placentae

2 20 *Concealed Hemorrhage*

A concealed hemorrhage is an accumulation of blood within the uterus or amniotic sac associated with abruptio placentae

2 21 *Placenta Previa*

Placenta previa is the implantation of any part of the placenta in the lower part of the uterine segment The term expresses the anatomic relationship between the placental site and the lower uterine segment The placenta encroaches on or covers (completely or partially) the internal cervical os Placenta previa is classified as marginal partial or total

2 22 *Marginal Placenta Previa*

Marginal placenta previa is present when some part of the placenta is attached to the lower uterine segment and extends to but does not cover any part of the internal cervical os

2 23 *Partial Placenta Previa*

Partial placenta previa is present when any part of the placenta incompletely covers the internal cervical os

2 24 *Total Placenta Previa*

Total placenta previa is present when any part of the placenta completely covers the internal cervical os

2 25 *Abortion*

Abortion is the expulsion or extraction from its mother of a fetus or embryo weighing 500 g or less (approximately equal to 20 completed weeks (140 completed days) to 22 completed weeks (154 completed days)) of gestation or an otherwise product of gestation of any weight and specifically designated (e g hydatidiform mole) irrespective of gestational age and whether or not there is evidence of life and whether or not the abortion was spontaneous or induced

ANNOUNCEMENTS

An International Symposium on Genito-Urinary Trichomonasis will be held in Paris 8–9 July 1977

For all information please address to Doctor A Fari S I T G U 5 Blvd de Strasbourg 75010 Paris France

The Fourth UICC Training Course in Cancer Research arranged by the International Union Against Cancer will take place on 4–17 September 1977 in Budapest

For further information write Dr László Holczinger Research Institute of Oncopathology 1122 Budapest Ráth Gy str 7 Hungary

The XVI Congress of the Spanish Fertility Society and International Symposium on Cervical Factors organized by the Spanish Fertility Society in Barcelona will take place on the 1st 2nd 3rd 4th and 5th November 1977 *Please note that the dates have been changed* Official reports Endoscopy on fertility Andrologic diagnoses and natural methods of family planning Round Table and courses for postgraduates

For further details apply to Secretary General Dr Louis C Pous Ivern Calle Muntaner 292–294 prol 1a Barcelona 6 Spain

Conference on the biology of
day international workshop con
Montreal in May 1978 An
ference will be to acquaint clinicians w
regarding our understanding of connective
ground substance while allowing
greater insight into clinically important
the incompetent cervix induction of labor and
dilatation for induced abortion To achie
plinary approach we solicit
in the biochemistry physiology and anatomy of
tive tissue as these relate to the
dilatation and from workers in
who are measuring the forces of dilatation
new types of dilators study
vical dilatation or related areas of investigation
expenses will be paid for invited participants
welcome at any time Abstracts should be
December 1 1977 to Phillip G Stubblefield
ton Hospital for Women 221 Longwood Avenue Bo
Mass 02115 USA or Frederick Naftolin M D
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Acta Obstet Gynecol Scand 56 255–256 1977

Letter to the Editor

of pain in primary dysmenorrhoea by noceptor stimulating drugs

recent report in this journal on the use of uprine in essential dysmenorrhoea (6) the au concluded that β adrenoceptor stimulation is ctive in releaving menstrual pain This con n was based on the results of a double blind olled clinical trial of isoxsuprine The patient ial of the investigation was limited consisting women of whom 26 completed the trial No on the gynaecological status of the patients given and only one dose regimen of isoxsu (?0 mg×3) was tried

r obvious reasons the results obtained in this cannot be accepted as evidence for lack of relieving effect of β adrenoceptor stimulators mary dysmenorrhoea In previous studies of en suffering from this condition it was found the myometrial activity was increased com d with that found in normal women (1 2 3 7) as also demonstrated (2) that the uterine blood decreased in association with the increased metrial activity and that the pain was probably ed by uterine ischemia (see also Fig 1)

is well known that the myometrium contains noceptors of β_2-type and that stimulation of e receptors results in relaxation of the uterus drenoceptor stimulators have been increasingly d clinically for depressing uterine activity in pregnant uterus (for ref see (4)) In both nor non pregnant women (1) and in women with nary dysmenorrhoea (2) the selective β noceptor stimulator terbutaline was found to uce the uterine activity and increase the uterine od flow When this occurred in the women with menorrhoea they reported complete relief of n (Fig 1)

Thus there is evidence that β_2 adrenoceptor nula ion can relieve menstrual pain effectively wever a prerequisite for this effect is that the

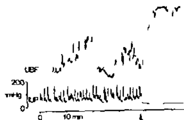


Fig 1 Uterine blood flow (UBF) intrauterine pressure (IUP) and the effect of terbutaline (0 5 mg i v injection indicated by arrow) on the first menstrual day in a women with severe primary dysmenorrhoea One minute after the injection the patient reported total pain relief (From Åkerlund et al Br J Obstet Gynaecol *83* 673 1976)

β-adrenoceptor stimulator used reaches the uterus in sufficient amounts There was no proof of this in the study cited above (6) In our opinion therefore the conclusion that can be drawn is not that β adrenoceptor stimulation is ineffective for releav ing menstrual pain but that isoxsuprine in the dos age used probably lacks a therapeutic effect in this condition

Unfortunately because of their side effects primarily tremor the β adrenoceptor stimulators presently available seem to be unsuitable for treat ment of primary dysmenorrhoea (2 5)

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FESTSCHRIFT

to

PROFESSOR

Axel Ingelman-Sundberg

in Recognition of

his Professorship in

Obstetrics and Gynecology

at Karolinska Institutet

and

his Chief Editorship of

Acta Obstetricia et Gynecologica

Scandinavica



AXEL INGELMAN-SUNDBERG

When Axel Ingelman Sundberg on July 1st 1977 leaves the post of Chairman of the Department of Obstetrics and Gynecology at the Sabbatsberg Hospital he *will be able to look back with great satisfaction upon a long period of fruitful* work including research education and medical service

Ingelman Sundberg obtained a sound obstetrical and gynecological training under Professor Axel Westman who had a unique ability to stimulate his disciples to scientific work To work in this research environment was highly encouraging and turned out to be an excellent foundation for future chairmen of womens clinics at universities and general hospitals

From a scientific point of view Ingelman Sundberg has treated a number of problems within the sphere of obstetrics and gynecology Thanks to an unusual technical and surgical capability combined with a creative imagination he has enriched the speciality with several important methods of treatment particularly in the urological area He has deepened our knowledge in this field via anatomic and roentgenological observations and has made a great contribution with his investigations into the cause and treatment of urinary incontinence urethro-vaginal vesico-vaginal and recto-vaginal fistula From these findings he has *worked out ingenious surgical methods for the healing of incontinence* conditions whether they be caused by sphincter damage pelvic floor insufficiency fistulas or nerve damage

He has moreover been a successful scientist in other fields of research and together with experts in pharmacology endocrinology and medical biophysics made interesting discoveries In the long row of publications prominance should be given to a penetrating analysis of the role of vitamin E among other things for sexual functions placental development and sperm formation

In a series of investigations the muscles of the uterine wall and in the tube have been studied during various phases of the menstrual cycle and during pregnancy Of special interest is the discovery that there is a sphincter like type of contraction around the uterine ostia which lacks an anatomically established foundation for a sphincter effect In close connection with these investigations the effect of various compounds on the motility in pregnant and non pregnant uterus as well as in tubes has been registered thereby adding to our knowledge of the therapeutic value of these compounds under different conditions

Ingelman Sundberg s name is widely known among gynecologists all over the world especially through his active engagement in international collaboration For a number of years he has been co-operating in the International Federation of Gynaecology and Obstetrics (FIGO) and for several years belonged to their Executive Board representing the Scandinavian countries besides serving for a period as their Vice President He has now been given the important mission of serving as Chairman for the FIGO Program Committee which has been allotted

the responsible task of organizing the scientific activities at the Ninth World Congress of Gynaecology and Obstetrics in Tokyo 1979

He has also engaged energetically in the publication of journals mainly as editor or co-editor for instance of *Acta Obstetricia et Gynecologica Scandinavica International Journal of Fertility* and *International Journal of Gynaecology and Obstetrics* Ingelman Sundberg s great organizing and administrative ability has appeared to advantage here and under his leadership the journals have developed very favourably

For Swedish gynecology too he has found time for stimulating work especially as President of the Swedish Gynecological Society and in its union organization the Swedish Medical Association

As an adviser to young clinical scientists and as a teacher of future physicians his time has also sufficed to attract the young generation to our subject area A clear sign of this activity has been the long string of doctor s dissertations emanating from the Department of Obstetrics and Gynecology at the Sabbatsberg Hospital during his time as Chairman of the Clinic

When Ingelman Sundberg now ends his career as Professor and Head of the Sabbatsberg Women s Clinic many thoughts of appreciation and gratitude will go to him from colleagues and disciples in the hope that he will still be able to make valuable contributions to our speciality I am convinced that a great number of foreign gynecologists will likewise express their great appreciation of his international achievements

Ulf Borell

It is a great pleasure for Danish obstetricians and gynaecologists to honour Axel Ingelman Sundberg on his retirement from the Chair of Obstetrics and Gynaecology at the University of Stockholm and the position as head of staff at the Sabbatsberg sjukhus

It is not our task to praise Ingelman Sundberg s great importance within his sphere in Sweden Our tribute is paid to him as the excellent chief editor of *Acta Obstetricia et Gynecologica Scandinavica* His predecessor as editor in-chief Professor Alf Sjövall had succeeded in placing the periodical on a very high level and it is Ingelman Sundberg s merit that during his editorship the journal acquired a still firmer foundation and its quality and world wide distribution were not only consolidated but also improved and increased to the benefit of Scandinavian obstetrics and gynaecology

Danish colleagues are also indebted to Ingelman Sundberg for his efforts to

spread knowledge of Scandinavian research and attitudes especially within the International Federation of Gynaecology and Obstetrics

During his term of office Ingelman Sundberg has received many Danish colleagues in the clinic and laboratories of the Sabbatsberg Sjukhus and many more have benefited from his papers read at Scandinavian congresses where colleagues had the chance of getting to know him personally and many have become his friends We are all united in thanking him

Mogens Ingerslev Dyre Trolle

The International Federation of Gynaecology and Obstetrics (FIGO) was founded in 1954 and since then many Scandinavian gynecologists have participated in the work of the Executive Board and the special committees of FIGO Of these eminent gynecologists Axel Ingelman Sundberg has of course been the most active and most appreciated by FIGO Having participated successfully in the work of both the Executive Board and the special committees of FIGO he was elected vice president of the federation during its VIIth World Congress in Moscow in 1973 In Bombay in 1975 he was also appointed associate editor of the *International Journal of Gynaecology and Obstetrics* which is the Official journal of FIGO During the VIIth World Congress in Mexico in 1976 Axel Ingelman Sundberg was appointed chairman of the committee preparing the scientific program for the 1979 congress in Tokyo

Twenty years have passed since the foundation of the Federation and FIGO is now firmly established Even though it is a non governmental organization with slender means its influence is increasing According to the first president and eminent general secretary of FIGO Professor Hubert de Watteville it is only through active co operation between the Executive Board and all the affiliated societies that the aims of FIGO can be reached Axel Ingelman Sundberg has been and still is a very valuable and active officer of FIGO who has both kept Scandinavian gynecological associations informed of the main activities of the Federation and provided FIGO with information about scientific activities in Scandinavia that are suitable for the Federation s scientific program For instance Scandinavians have been much more numerous as main lecturers at FIGO World Congresses than one would expect from the number of gynecologists in Scandinavia This of course is due mainly to the high scientific standard of Scandinavian papers which is generally known but the active participation of Axel Ingelman Sundberg as a FIGO officer has certainly spread the knowledge of

Scandinavian scientists among the scientific committees of FIGO All the friends of Axel Ingelman Sundberg here in Scandinavia are very happy that he will be continuing his activities in FIGO after retiring from his chair His vast experience scientific mind and good administrative judgement are needed to keep Scandinavian gynecologists and their scientific work as well known in FIGO as they are now

Lauri Rauramo

Acta Obstetricia et Gynecologica Scandinavica has been a major scientific forum for gynecologists in the Nordic Countries for more than half a century

Acta s fame and reputation as well as its circulation have continued to increase through the decades and it has by now attained great respect within our specialty throughout the world

Acta has been blessed by good fortune right from the beginning The chief editors have come from the ranks of the best scientists within our special field well known within the Nordic Countries as well as internationally

It has been the responsibility of the chief editors to raise *Acta s* standards to mould and to adapt it to the demands of each period

Now that Professor Axel Ingelman Sundberg is resigning from his post as chief editor of *Acta Obstetricia et Gynecologica Scandinavica* it is my pleasure on behalf of gynecologists in Iceland to express our gratitude for the many years of excellent and beneficial service he has performed in the interests of the field of gynecology as well as for his outstanding administrative capabilities

Gunnlaugur Snædal

Due to fruitful work in a wide spectrum of the medical field in his own country in joint Scandinavian collaboration and at an international level Axel Ingelman Sundberg has occupied a central position among Scandinavian gynaecologists for years His achievements in Swedish medicine will be covered elsewhere I would like to add that his initiation of gynaecological health control and of organized pediatric service at the obstetrical departments in Sweden deserves general recognition

Axel Ingelman Sundberg was first known among his Scandinavian colleagues through his steadily increasing number of papers of common clinical and scientific

interest published in the Scandinavian journals *Nordisk Medicin* and *Acta Obstetricia et Gynecologica Scandinavica*

As a member of the Scandinavian Association of Obstetricians and Gynaecologists from 1950 he has been an unfailing attendant and a highly active participant at the congress meetings From 1950 to 1960 his name appears fifteen times among contributors to the official transactions of the Association The characteristic feature of his medical activity has been the broad spectrum of his interests He has made significant contributions to *Acta Physiologica* (1) *Acta Endocrinologica* (5) *Acta Radiologica* (2) *Acta Chirurgica* (4) and *Acta Obstetricia et Gynecologica Scandinavica* (30) frequently working in close collaboration with experts in other fields

Behind his often very sophisticated research work we can trace the solid foundation of a devoted and experienced clinician a hall mark which has always been highly appreciated in Scandinavian medicine

In 1968 he servd as president of the Scandinavian Association of Obstetricians and Gynaecologists in Stockholm

His achievements in the urological field of interest for obstetricians and gynaecologists are of great theoretical and practical importance a well recognized Scandinavian contribution to international medicine

A great deal of his research activity deals with basic problems in fertility and it was only natural that he was one of the founders of the Scandinvian Association for Studies in Fertility (1959) designed as a meeting place for physicians veterinarians and others interested in reproductive problems This has proved to be a very vital organization indeed with Axel Ingelman Sundberg as an unfailing and enthusiastic participant He served as president in 1961 and 1974 and was recently elected an honorary member of the Association

Axel Ingelman Sundberg succeeded Alf Sjovall as chief editor of *Acta Obstetricia et Gynecologica Scandinavica* on the 1st of July 1970 and resigned on the 1st of April 1977 This has been a period of accelerating research activity characterized by new techniques and new methods of approaching the problems The period has placed heavy demands on the chief editor who has the main responsibility for preserving the tradition of our *Acta* as a highly respected and trustworthy medical journal Axel Ingelman Sundberg had the necessary scientific qualifications the ability to analyse scientific data critically and the sound medical judgement to meet the challenge and *Acta Obstetricia et Gynecologica Scandinavica* is still one of the leading medical journals on clinical research Another main editor problem during this period has been the vast number of papers presented for publication In his unique position as editor of the *Acta* and associate editor both of the *International Journal of Gynaecology and Obstetrics* and of the *International Journal of Fertility* and as editorial consultant of *Medical*

Gynaecology Andrology and Sociology Axel Ingelman Sundberg has rendered Scandinavian research workers a valuable service by providing access to these journals and strenthening the possibility of a Scandinavian impact on international medicine The acceptance of a small group of excellent papers from other countries in return has underlined the high quality of the *Acta*

The improvement in typographical standards and the establishment of a sound financial basis for *Acta* also deserve to be mentioned among the achievements which should be credited the organizing and administrative talents of Axel Ingelman Sundberg

We can safely conclude that his leadership of *Acta* has served our international *reputation in a highly successful way*

This tribute to Axel Ingelman Sundberg would be very incomplete without any reference to his colourful personal qualities His Scandinavian colleagues know that his resignation from the posts of chairman and chief editor does not mean that his vitality has been reduced only redirected We wish him luck in his future Scandinavian and international engagements

Oddmund Koller

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A SCHEME OF PREGNANCY MANAGEMENT

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...is management of pregnancy the obstetrician ...ries about the condition of the fetus and indi...ual factors influence his judgment Nevertheless ...ay be useful to have some basic rules about the ...ice of available tests (1)

...ur knowledge of reproductive physiology has ...n thoroughly tested by the use of these diagnos... tests and found to be satisfactory enough

...scheme of management must be rational but ...nple it *must be able to be carried out in less* ...ll-equipped hospitals and it must take all preg...ncies into account not only the ones which ...ording to often arbitrary criteria are considered ...gh risk pregnancies Three different steps are ...vided for outpatient screening short term ...pital check-up and long term hospital evaluation ...d treatment

The different parts of the scheme will be dealt ...h one by one

FETAL GROWTH ASSESSMENT

...upled with placental function evaluation this is ...main point of the scheme The clinical assess...nt of fetal growth by periodic measurement of ...e fundal height is at least *for the time being* ...ficiently reliable Repeated ultrasonic screening ...all pregnancies is at present practically impossi...e

The ultrasonic assessment will therefore be re...rved only for

1) The cases *in which* the maternal condition or ...ny actual disease leads one to expect the theoreti...al possibility of poor fetal growth

2) The cases in which the clinical assessment of ...tal growth is uncertain

3) The cases in which poor fetal growth has already been clinically diagnosed

4) The cases in which poor fetal growth has already been diagnosed both clinically and ultrasonically and in which the growth rate is to be followed particularly during and after treatment

As for the ultrasonic measurements to be chosen we would suggest both the biparietal diameter (2) and trunk (3) (chest or abdomen) (4) circumference *and the assessment of their growth rate in order (a)* to see whether poor fetal growth is proportionate or disproportionate and (*b*) to follow the patterns of the two different measurements both for prognosis and for judging the effects of treatment

Generally the time for ultrasonic assessment will be imposed by different conditions and circumstances rather than chosen Of course it should be as early as possible considering that the most convenient time for measuring the diameter and for estimating its growth rate is maintained to be between the 20th and 30th week

ESTABLISHMENT OF GESTATIONAL AGE

This problem is often connected with that of fetal *growth In fact apart from the cases in which gesta*tional age cannot be determined on the basis of menstrual history alone (about 15–22%) there are cases in which the clinical and ultrasonic assessment have provided values lower than expected so that the alternatives are either real poor fetal growth or wrong gestational age (5)

Gestational age can be determined by comparing the ultrasonically measured diameter with the figures shown in the well known intrauterine growth charts (6) For this purpose the ultrasonic predic

tion of gestational age by measuring biparietal diameter is best accomplished between the 20th and 30th week and is still valid between the 30th and 34th Later on the growth rate is slower the variability of results is increased and therefore the test becomes much less valuable

We have already mentioned that even when one knows or believes one knows the gestational age if values much lower than expected are obtained it is necessary to confirm whether it is a problem of incorrect gestational age determination or poor fetal growth To this end one can resort to a comparison between two ultrasonic measurements obtained one or two weeks apart from each other then comparing *the weekly and the expected growth rate If the* two correspond a mistake in determining gestational age will be proved If the weekly growth rate turns out to be less than expected poor fetal growth will be assumed (7) Proper charts are available for this specific growth rate For this purpose assessment before the 30th week is also recommended

PLACENTAL FUNCTION EVALUATION

Coupled with fetal growth rate placental function evaluation is the basis of the scheme Among the different available tests the most useful are hormonal assays and antepartum cardiotocography

Placental function can be ascertained both by basic and dynamic tests

(a) *Basic tests*

The first assessment of basic placental function in l pregnancies is accomplished through ekly estrogen determination (HCS is seldom) Plasma estriol assay (8) is very helpful in cases nevertheless practical problems are to be expected like the refusal of the patient to provide weekly blood samples her annoyance about reaching the clinic (sometimes far away) at fixed times and waiting for her turn and difficulties in organizing the venepuncture service which is often very busy

Despite some objections about renal clearance (9) postural variations (10 11) and circadian rhythm (12 13) we believe that the urinary estrogen determination is suitable for practical purposes

From our experience (14 15 16 17 18) with *more than 9000 assays on 2½ hour urinary samples* estimating the estrogen/creatinine ratio we can confirm the reliability of this method Should we think of changing anything this would not be biological medium but the analytical procedure fact the spectrographic method (Ittrich) em ing the Allen equation involves pigment inter ence and the smaller the quantities of the estrogens the more and more distorted are th results

Furthermore analytical procedures like drolysis extraction and purification bring a an estimated loss up to 50% This is why for s time we have been employing the radioimmun say using Davis Loriaux s (19) antiserum for Estriol 16 glycuronate in urinary samples out any need of preliminary hydrolysis (20)

The weekly determination is performed st from the 24th week The values are expressed index taking gestational age into consideration Index values below −10 are regarded as abn Persistently low values or precipitous falls of 25% require admission to hospital for diagn and therapeutic measures

Strict monitoring is *accomplished by* dail nary estrogen assays on hospital patients procedure using short collection allows us t peat the determination many times in the sam (theoretically 9 times in 24 hours) and to conf within 6 hours whether the falling levels persist whether there really is a precipitous fall This is of particular importance considering *the wide* variation of estrogen level

(b) *Dynamic tests*

Dynamic placental tests are very valuable alth there are still considerable doubts about how so of them work (22 23) They include

1) Estrogen gain 17 beta-estradiol gain after DHA S load to the mother or by the intraamn route (24 25 26 27)

2) Estrogen gain after progesterone adm tion (28 29 30)

3) Antepartum cardiotocography fetal heart (31) step test (32) oxytocin challenge *test* (33)

4) Fetal electrocardiography (34 35)

The results of antepartum cardiotocography scored employing a suitable system (36) T dynamic tests are performed on hospital patient They are selected and compared with one anoth The hormonal ones are usually done after 3 day bed rest Usually they are not repeated Cardio cal tests on the other hand are usually done week

FETAL MATURITY ASSESSMENT

erous valid methods for the biochemical as ment of fetal pulmonary maturity are available idays Among the different procedures like thin L/S ratio (37) Clement test (38) (shake or n test) total phospholipide phosphorus assay lecithin assay (40) we have adopted the first (L/S ratio) following Gluck s original method According to Dunn & Bahtnagar (41) L/S s greater than 2 are defined as mature those or less immature ratios between 1 and 2 are d transitional Using this method we always ved a good agreement with the neonatal out e as far as the risk of respiratory distress is erned (4?) On the basis of our own experience ses with delayed lung maturity even at the 38th 39th week particularly when maternal diseases diabetes are present we extend the practice of nonary maturity assessment to all the cases it to undergo planned delivery (43)

TREATMENT OF FETO-PLACENTAL *INSUFFICIENCY*

the above combination of clinical ultrasonic moral and cardiotocographic methods we reach agnosis of the feto-placental status If this is im ed treatment becomes necessary Although the ilts of fetal treatment in utero are promising as cribed in the International Parma Symposium on ie therapy of feto-placental insufficiency (44) believe that the *best policy is still to deliver* se fetuses as soon as possible Nevertheless n the gestational age or fetal maturity tests ecially those concerning lung maturity indicate a ous neonatal risk there is no alternative to fetal atment By this we mean drug treatment improv placental blood flow (45) i e vasodilatators (46 tocolytic (48 49 50 51) or antithrombotic ag s (5? 53 54) as well as bed rest and the treat nts which are *required for any* maternal disease At present another possibility is to accelerate al lung maturity by administering gluco-corti ids at least ?4 hours prior to delivery (55 56 57 59) The total dose is around 36 mg of dexa ethasone given in 3–5 days or all at once After 3?nd week the administration can precede the ng maturity test hence the glucocorticoid will be ven before amniocentesis

PLANNED DELIVERY

This is reserved for cases showing precipitous falls *in the estrogen level or impaired dynamic tests* always after assessing fetal lung maturity

However even cases with quite normal fetal condition but with an immediate or assumed high risk can undergo planned delivery of course after checking the fetal lung maturity Planned delivery can be vaginal or abdominal depending on the indi cations or the clinical findings or the results of dynamic placental tests (especially the oxytocin challenge test) Recently our cesarean section rate has been fairly high adding those with planned de livery to those with traditional indications it is over 16%

Thanks to a better experience especially with antepartum and intrapartum cardiotocography we think we may be able in the future to reduce this percentage

INTRAPARTUM FETAL HEART RATE AND ACID-BASE BALANCE

It would be convenient for intrapartum cardiotoco-graphy to be extended to every case even if nor mal However it is essential at least in those in cluded in the group of planned vaginal delivery and when the above scheme has showed a condition of *fetal risk (60 61) In these cases* labor will be man aged by assessing acid base balance (62)

PROCEDURE

The two most important criteria assessed in this scheme are fetal growth rate and placental function (Fig 1)

Usually the former has been assessed clinically by determining uterine size at the first consultation during the 1st trimester and then estimating growth at intervals The hormonal evaluation of placental function by urinary estrogen assay is theoretically *useful only from the 24th–26th week onwards*

At this stage of pregnancy possible doubts about gestational age should already have been removed and any poor fetal growth diagnosed even if growth defects are more frequently evident during the third trimester Cases of poor fetal growth as well as those with impaired placental function are bound to undergo dynamic tests and strict monitoring and they will therefore be in hospital The same proce

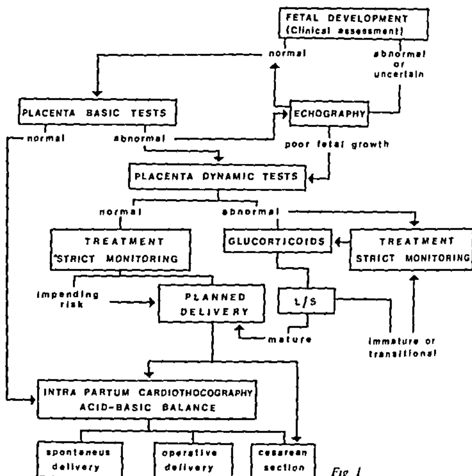


Fig 1

dure is used in the so called high risk cases whether the risk is estimated from the history or from the mothers present condition Cases with reassuring dynamic tests and monitoring data will be able to go as far as term or planned delivery

Those showing very abnormal dynamic tests or a precipitous fall in the course of strict estrogen monitoring must undergo planned delivery more or less quickly according to the circumstances At this moment gestational age will play a role of great importance in the choice of method for delivery We suggest the utmost care when estimating fetal maturity better not to rely upon gestational age only[1] From the 32nd week the amniotic fluid L/S ratio should be calculated at least 24 hours after dexamethasone administration If the baby is judged to be mature delivery will be planned The most difficult problems to be resolved are cases with an impending risk and fetal immaturity We have always continued the treatment of placental insufficiency until adequate fetal lung maturity has been attained This policy has never resulted in fetal death so far and at the same time we have [illegible] observed any respiratory distress in the babies [illegible] by planned delivery Obviously this scheme [illegible] others of the same kind can be labelled as [illegible] and at the same time defective We think that [illegible] experienced and sensible obstetrician can [illegible] and verify its real usefulness We hope that a [illegible] and larger number of hospitals and centers will [illegible] able to organize and maintain a scheme of management like the one we have described

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PREGNANCY INDUCED HYPERTENSION

1 *Role of Sympathetic Nervous System and Adrenal Gland*

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-ateral adrenalectomy in the female results in a de -e in the urinary excretion of epinephrine by 80% io change in the excretion of norepinephrine (1) It -be assumed that the urinary excretion of epinephrine relative measure of adrenal secretion of this neuro- f ione and the excretion of norepinephrine is primarily lection of sympathetic nervous system activity -vels of epinephrine and norepinephrine can be al -3 by physical activity and the differences in excretion l in relation to the activity of the patient i e bed s moderate activity or strenuous activity Addition diurnal variations in excretion of epinephrine and pinephrine also occur with a decline in both at night (? 3)

revious studies from my laboratories have shown that -ary catecholamine excretion can be used as an indi of stress in pregnancy Despite the physiologic hor al biochemical and anatomic changes that occur in gnancy it has been shown that alterations in epi -hrine and norepinephrine are not stressful antepartum se studies were done in ideal conditions utilizing the e group of patients over a protracted period of time -partum intrapartum and postpartum for as long as consecutive months The values of epinephrine were ilar antepartum and during labor and postpartum vever the only positive finding was an increased ex tion of norepinephrine the day following delivery (4) se findings have been confirmed by Goodall & Diddle o concluded that normal pregnancy and labor have no ificant effect upon the adrenal medulla in respect to nephrine and norepinephrine (5)

This report assimilates the past data that I have pub- ied as well as that of others in identifying that the enal gland and sympathetic nervous system are al ed in toxemia of pregnancy known as pregnancy in ced hypertension or preeclampsia

MATERIAL AND METHODS

e literature has been surveyed pertaining to other idies that have identified epinephrine and norepineph e in comparing normal pregnancy to preeclampsia ly those studies in which individuals were studied in normal pregnancy and preeclampsia will be included in this report since isolated studies of preeclampsia alone are of less value

Analysis for epinephrine and norepinephrine

The method used in my laboratory to determine free urinary epinephrine and norepinephrine has been pre viously described (6) The method utilizes fluorometry in the trihydroxyindole procedure whi h is automated and measures principally epinephrine at pH 3 5 and only nor epinephrine at pH 6 5 Over the years this method has been modified and now includes a radioactive tracer for sample column recovery with all results corrected to 100% to account for column loss The urine is deprotein ized with perchloric acid and the free urinary epinephrine and norepinephrine are absorbed onto alumina and later eluted with a weak acid The eluate sample which is approximately pH 3 is adjusted to pH 6 for thioglycolic acid to determine norepinephrine or to pH 3 5 for use with ascorbic where both epinephrine and norepinephrine fluoresce The percent recovery of the columns are 75% plus or minus 5% Blanks are determined at both pH 3 5 and 6 by substituting water for either thioglycolic or ascorbic acid The automated method requires a sampler proportioning pump system fluorometer and sensitive recorder to measure fluorescence Results are calculated and are usually expressed in micrograms of epinephrine and norepinephrine for 24 hours or in micrograms per hour

DISCUSSION

The human adrenal medulla contains both epineph rine and norepinephrine of which 90% is epineph rine Norepinephrine is the neurohormone of the sympathetic nervous system Both of these hor mones are excreted in the urine in quantities that parallel the sympatho-adrenal medullary activity Normally during a 24 hour period the urinary ex cretion of epinephrine is less than 20 micrograms and usually approaches 10 micrograms Norepi

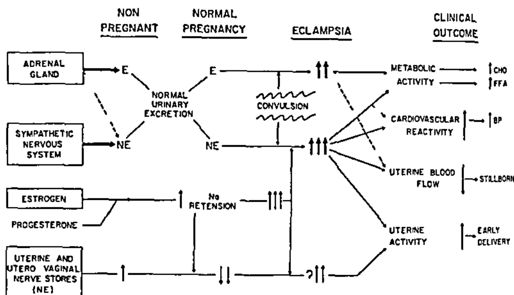


Fig 1 Interaction between adrenal gland sympathetic nervous system ovarian hormones and different uterine nerves in the pregnant and non pregnant patient Zuspan F P Am J Obstet Gynecol *114* 304 1972

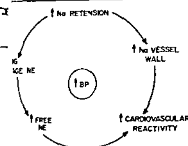
nephrine during this same period of time is less than 50 micrograms The quantities of urinary excretion of epinephrine and norepinephrine during pregnancy compared to the non pregnant state is similar in the antepartum period

Studies in the past have often been done on randomized urine samples in different patients however sequential studies on the same patient under similar conditions decreases the tendency for individual variation in urinary amines These studies on the same group of patients under similar controlled environmental conditions were done to establish aseline values for normal pregnancy These find gs essentially show no change between the pregnant and non pregnant state during the antepartum or the postpartum period for either epinephrine or norepinephrine except for an increase in norepinephrine in the first 24 hours postpartum indicating late labor and delivery activity

Preeclampsia pregnancy induced hypertension or toxemia are terms that are used interchangeably This broad clinical spectrum of unknown etiology makes it difficult to compare one patient to another and even more difficult to compare one investigator s patients to another investigator s patients This clinical disease spectrum helps identify some of the confusion and occasional contradictory findings seen in this disease

The sympathetic innervation of the reproductive tract demonstrates two types of nerves One is a long adrenergic neuron that originates from a paravertebral ganglion The second type of short adrenergic neurons originate in the immediate vicinity of the effector organ (7) It has been demonstrated in the guinea pig that a decrease adrenergic transmitter in uterine nerves is seen in late pregnancy (8) The question that has not been answered is what happens to these short nerves in the human in late pregnancy More particularly what happens to them in pregnancy induced hypertension and even more particularly in eclampsia Animal studies cannot answer the question since no complete animal model exists for pregnancy induced hypertension

It is known that catecholamines have a metabolic cardiovascular and local effect upon the uterus as well as upon other systemic organ systems in the body Norepinephrine produces peripheral vasoconstriction and additionally has an oxytocic effect upon the gravid uterus (9) Zuspan (10) has proposed a schematic interaction (Fig 1) between the adrenal gland sympathetic nervous system with the effect of ovarian hormones and the type of uterine and uterovaginal nerves in the non pregnant normal pregnant and eclamptic state This schema emphasizes the clinical outcome seen in the most severe of acute pregnancy induced hypertensive disease eclampsia He has demonstrated a marked increase in both urinary epinephrine and norepinephrine that occurs on the d



Proposed relationship between sodium balance pressure and neurotransmitter (NE)

onvulsion The increase persists after the con on and is often enhanced by delivery when it rs close to the time of the convulsion There some epinephrine and norepinephrine values ese 14 eclamptic patients in which the levels oached that seen in a pheochromocytoma No r such reports are in the literature (10)

issue of concern in patients that have preg y induced hypertension is to consider the role pinephrine and norepinephrine in relation to ges in cardiovascular reactivity We have stud he cardiovascular sensitivity and reactivity to ions of angiotensin Norepinephrine and epi nine demonstrate hyperreactivity in patients have preeclampsia (11) It was postulated at time that the increased sodium in the vessel may account for the altered vascular reactivity area needs further investigation in trying lemonstrate the relationship between sodium nce blood pressure and the neurotransmitter pinephrine (11) There is a decreased ability he sympathetic granules to bind and store nor ephrine when sodium is in excess (Sodium is in ess in preeclampsia) If there is reduced capac for binding and storage this might make more ilable free circulating norepinephrine The pa t s own amines could react on receptor sites and rease the cardiovascular reactivity This could as a positive feedback mechanism for the de opment of hypertension (Fig 2)

rior to the above study Zuspan Nelson & Ahl st (17) demonstrated an increased cardiovascular ctivity to an ... of epinephrine in mild pre ampsia (Fig 3) The question as to whether or t milder forms than eclampsia will be associated th the disruption of homeostasis of the neuro rmones seen in normal pregnancy needs further

Table I

	Epi nephrine (µg/h)	Norepi nephrine (µg/h)
Normal antepartum (balance ward hospitalized)	*0.21*	*1 16*
Controls		
1st 1? hours ho pitalized	0 97	0 84
2nd 1? hours hospitalized	0 43	1 45
3rd 12 hours hospitalized	0 51	0 64
Mean	*0 64*	*0 98*
Pregnancy induced hypertension moderate severity		
1st 1? hours hospitalized	1 97	1 64
?nd 12 hours hospitalized	1 68	1 72
3rd 1? hours hospitalized	1 31	1 49
Mean	*1 65*	*1 62*

clarification Urinary amine excretion during preg nancy has been investigated by Pekkarinen & Castren on 31 patients with severe preeclampsia compared to 310 normal patients utilizing the measurement of urinary vanilmandelic acid (VMA) There was no difference in the groups excretion of this substance and it was concluded that this was an insensitive endpoint measurement between the two groups (13)

Cession demonstrated that urinary levels of epi nephrine norepinephrine and vanilmandelic acid are significantly higher in severe preeclampsia than in normal pregnant women and that the magnitude of response was somewhat proportional to the se verity of the disease (14) Zuspan has confirmed

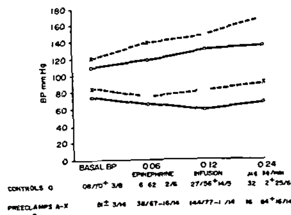


Fig 3 Data modified from previous study of Zuspan et al demonstrating altered cardiovascular reactivity to epinephrine (Zuspan F P Nelson G H & Ahlquist R P Am J Obstet Gynecol 90 9? 1964)

Table II *Cardiovascular reactivity*

	Response to infusion of	
	Epinephrine	Norepinephrine
Non pregnant	+	+
Normal pregnant	+	+
Preeclampsia	++	+++

these findings in which controlled patients were compared to preeclamptic patients when they are first admitted to the hospital for 12 hour periods of observation Table I illustrates that in normal ante partum patients under balance ward conditions the epinephrine was 0 21 micrograms per hour con trasted to controls in the study mentioned above of 0 64 which is compared to moderately severe pregnancy induced hypertension of 1 65 The nor epinephrine values also show a similar trend in that normal antepartum (balance ward) was 1 16 the controlled study was 0 98 and the patients with pregnancy induced hypertension was 1 62 (15)

The amount of vascular reactivity correlates well with the severity of pregnancy induced hyperten sion (Table II) The increased amine activities in pregnancy induced hypertension may be a factor that aggravates the disease It is impossible to state whether or not this is a cause and-effect relation ship since many co variables alter neurohumoral mechanisms To date no one has identified the reason for the increased amine excretion since it could be from changes in metabolism binding re ceptor activity and sodium balance We are left with . knowledge that there is increased amounts of . nephrine and norepinephrine associated with pregnancy induced hypertension Their role to date is yet to be determined

ACKNOWLEDGEMENT

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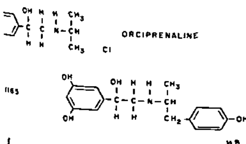
COMPARATIVE STUDY OF UTERO INHIBITING ACTION OF TWO β ADRENOMIMETIC DRUGS

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Gynecologist and Obstetrician frequently en ters problems in which the health of the fetus is itened by uterine activity Such uterine con ions occasionally occur after surgical interven in which the pelvic viscera have been manipu l, or because during labour one or several of the ponents of uterine activity are abnormally ex bated or when uterine contractility with normal acteristics interferes with the placental func

ie necessity of decreasing the uterine contrac when it threatens the wellbeing of the fetus has ght about the search for a pharmacological t which offers the greatest uterine inhibiting m with the fewest undesirable secondary effects ie best prospect lies in the use of β adreno- etic drugs Among these the one which has best studied in the Hospital de Gineco Ob- icia No Uno del Instituto Mexicano del Se Social is orciprenaline (4 5 6) Although this it is not the ideal uterine inhibiting drug it is known to us and as such has been taken as rameter of comparison for the other β-adreno- etic agents studied



In this paper we present thre results of the com parison between Th 1165 a and orciprenaline

Orciprenaline (C H Boehringer Sohn Ingelheim am Rhein Germany) 1 (3,5 dihydroxyphenyl) 2 isopropil aminoethanol hydrochcloride

Th 1165 a (C H Boehringer Sohn Ingelheim am Rheim Germany) 3 5 dihydroxy alpha {[(p-hy droxy alpha methyl phenetyl) amino] methyl} ben zylalcohol hydrobromide

PATIENTS AND METHODS OF STUDY

To date thirtyseven patients have been selected for study (17 for Th 1165 a) from the admission service of the Hospital de Gineco Obstetricia No Uno Patients have been selected to meet the following criteria

(*a*) Term pregnancy (38 to 4 weeks of amenorrhea)

(*b*) Systolic blood pressure between 100 and 140 mmHg and the diastolic blood pressure between 60 to 90 mmHg

(*c*) Parity greater than I and less than V

(*d*) No clinical manifestation of maternal or fetal pathology or cephalopelvic disproportion

(*e*) Early labour with cervical dilatation greater than 2 cm and less than 5 cm

(*f*) Membranes intact

In these patients continuous recording of intra amniotic pressure was made following the technique of Caldeyro-Barcia (1) in order to quantify the mod fications of uterine activity

Continuous recordings were also made of arterial pressure through a polyethylene catheter inserted into the abdominal aorta via the femoral artery (6) maternal heart rate by integrating the R waves of the maternal electrocardiogram (ECG) and fetal heart rate by integrat ing the modification on ultrasonic waves produced by the heart beats (Doppler s effect)

Maternal and fetal ECG tracings were recorded before and after administration of β-adrenomimetic drugs The maternal ECG s were taken with conventional electrodes and methods The fetal ECG s were taken with a conven

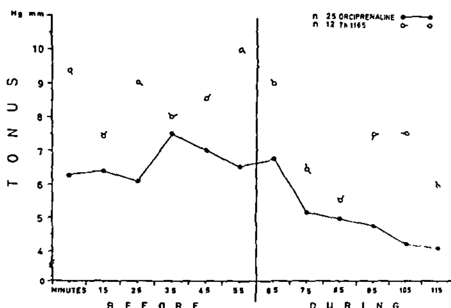


Fig 2

tional electrocardiograph using an Elemedix fetal ECG preamplifier and the scalp electrode of Hon (7)

All patients were given intravenously 0 03 μg of Th 1165a per minute per kilogram of body weight during 60 min the Th 1165 a was diluted in isotonic sodium chloride solution

Twenty five patients selected with the same criteria were given intravenously 0 28 μg of orciprenaline per minute per kilogram of body weight during 60 min. The orciprenaline was also diluted in isotonic sodium [illegible] solution

Maternal arterial blood samples and fetal scalp [illegible] blood samples were obtained at the beginning and [illegible] end of infusion for acid base balance glucose [illegible] pyruvic estimations

Table I *Uterine contractility Mean values of variables one hour before and one hour during Th 1165 a infusion (n=12)*

Variable	Th 1165 a (means) Before	During	P
Tonus	8 74	6 99	<0 05
Intensity	26 87	17 05	<0 005
Frequency	4 61	3 99	n s
Uterine activity	116 65	70 70	<0 005

Table II *Uterine contractility mean values of the variables one hour before and one hour during orciprenaline infusion (n=25)*

Variable	Orciprenaline (means) Before	During	P
Tonus	6 65	5 00	<0 005
Intensity	27 79	19 54	<0 005
Frequency	4 76	4 27	n s
Uterine activity	132 84	75 37	n s

RESULTS

For each treatment the values of tonus [illegible] and uterine activity were measured one hour [illegible] and one hour during the influence of the [illegible] These values were then analyzed

In the statistical analysis the great variability [illegible] sented by the different parameters within each [illegible] tient was taken into consideration This was [illegible] between patients of the same group and [illegible] groups

The means for each period of 10 min before [illegible]

Table III *Uterine contractility Comparison of [illegible] tables during infusion of two drugs orcipre[illegible] (n=25) and Th 1165 a (n=12)*

Variable	Drug infusion (means) Orciprenaline	Th 1165 a	P
Tonus	5 00	6 99	<0 01
Intensity	19 54	17 05	n s
Frequency	4 27	3 99	n s
Uterine activity	75 37	70 70	n s

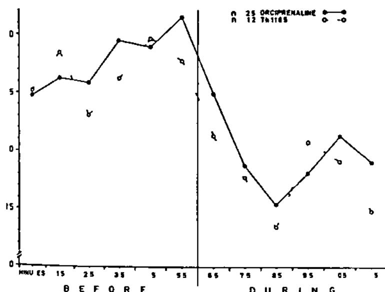


Fig 3

...ring infusion of the drugs were obtained The ...n for each phase of the two treatments was ...pared by means of Student s *t* test The results ...summarized as follows (Tables 1 2 3)

...onus The difference in the values of tonus be... and during the infusion are significant to a level ...05 for both drugs Tonus decreases more with ...prenaline than with Th 1165 a (Fig 2)

...tensity The decrease of intensity observed during the administration of the drugs is statistically significant and there is no appreciable difference between them (Fig 3)

Frequency No significant difference was found at the 0 05 level before and during the administration of both drugs there was no significant difference between the two drugs when their effects were compared (Fig 4)

Uterine activity In both groups uterine activity

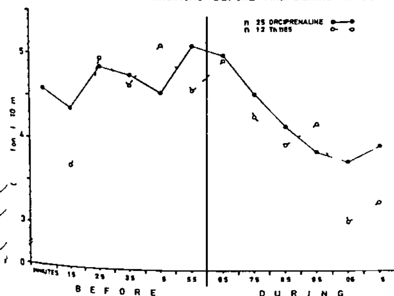


Fig 4

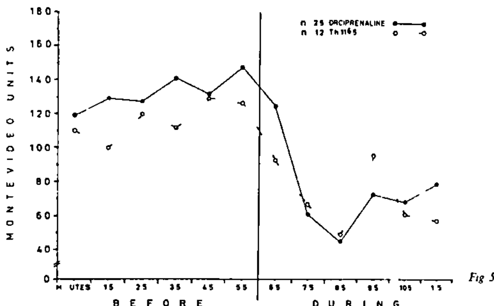


Fig 5

increased before the administration of the drug but decreased to 40% of its average value during infusion (Fig 5)

The difference is significant at a level of 0 005 There was no difference between the two drugs

The maximum action of orciprenaline on uterine contractility was reached at the 25th minute of infusion The largest uterine inhibitory effect with Th 1165 a was reached at the 15th minute

Apparently the decrease of uterine activity with the studied drugs corresponds to the decrease of the intensity since the frequency was not significantly modified with its administration The acid base bal[illegible] in patients under Th 1165 a infusion were similar to those found in patients receiving orciprenaline (2)

DISCUSSION

Our results for orciprenaline are in agreement with those reported by Poseiro et al (6) and Eskes et al (7) The data published by Gamissans et al (8) for Th 1165 a are similar to our results

The comparison of variables in uterine contractility with the above drugs given intravenously showed no statistical difference except for the tonus This could be due to the smaller number of cases studied with Th 1165 a

Both drugs diminish uterine activity by reducing the intensity of contractions

It can be observed that Th 1165 a has an e[illegible] lier and more persistent action than that [illegible] orciprenaline during the hour of infusion never[illegible] less a larger number of cases has to be studied [illegible] draw definite conclusions

Secondary effects on the mother such as arte[illegible] hypotension and tachycardia were less marked [illegible] the Th 1165 a series than in the orciprenaline [illegible]

The fetal tachycardia was also less severe [illegible] mother was given Th 1165 a than if she rece[illegible] orciprenaline

Among the uterine inhibitory drugs the β-adr[illegible] mimetic agents seem to have a very pro[illegible] future

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THE EFFECT OF SALBUTAMOL AND TERBUTALINE IN THE MANAGEMENT OF PREMATURE LABOUR

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tract A comparative study concerning the effect of utamol and terbutaline in the management of prema labour with intact membranes has been performed group in luded 34 patients between 27–36 weeks tion The drugs used were given by intravenous infu Salbutamol arrested labour activity in 33 of 34 pa ts and terbutaline in 32 of 34 patients Delivery was tponed for more than one week in 74% of the patients ving salbutamol and in 80% of the patients receiving utaline No significant difference in effect was found i the drugs used The effect was equally good ependent of the gestational age Dilatation of cervix ond ? cm was associated with successful treatment ay of delivery more than one week) in 27% compared 1% if cervix was dilated . cm or less In 12 patients 1 ruptured membranes a temporary arrest of labour ity (1 7 days) was obtained in 7 patients and in 1 ent the delivery was delayed for 6 weeks In the dos ed an increase in maternal and fetal heart rate was erved more frequently in the patients receiving ol compared with those receiving terbutaline serious side-effects were observed neither in the utamol nor the terbutaline group It is concluded that h drugs are well tolerated and effective in the treatment remature labour

e efficiency of β receptor stimulating adrenergic igs to inhibit uterine contractions is well docu nted The first clinical report concerning the icacy of these drugs in inhibiting uterine activity s published by Hendricks et al (6) Clinical fulness was however limited due to adverse e-effects i e tachycardia palpitations and tre r In recent years drugs with more selective mulatory effect on the β receptors which are ponsible for the inhibitory effects on uterine con ctions have become available Among these igs terbutaline has been shown to inhibit uterine ivity (1) and prevent premature delivery (7) Recent studies measuring the relaxing effect upon the pregnant human uterus in vivo have shown that another adrenergic β receptor agonist salbutamol was more effective than terbutaline in this respect (2) Clinical trials have also demonstrated that salbutamol is effective in inhibiting uterine contractions (10) and preventing premature delivery (9)

No comparative study concerning the clinical effect of these drugs in the management of premature labour has previously been performed The aim of the present study was to compare the effect of salbutamol and terbutaline in premature labour and to study the influence of these drugs on maternal and fetal heart rate and maternal blood pressure

MATERIAL AND METHODS

The study was performed during the period May 1974 to April 1976 The patients included in the comparative study fulfilled the following criteria Active uterine contractions with a frequency of at least two contractions every 10 min verified by means of external tocography over a period of about 30 min intact fetal membranes and a duration of pregnancy between .7 to 36 weeks Patients with ruptured membranes twin pregnancies or those who had been operated upon for cervical incompetence were excluded 34 patients received salbutamol and 34 patients terbutaline by random selection An analysis of the patients with reference to the state of the cervix the length of pregnancy and the frequency of contractions at the start of the treatment (Table I) ind cate that the groups were comparable in these respects A statistical analysis using Student s *t* test could not demonstrate any statistical differences between the groups

One group comprising 1? patients with ruptured membranes and labour activity have also been treated with salbutamol or terbutaline These patients are reported separately

The drugs were administered by intravenous infusion using an infusion-pump or a drip counter

Table I *Comparison of patient characteristics and treatment*

	Salbutamol	Terbutaline
Number of patients	34	34
Frequency of contractions		
<3/10 min	21	24
≥3/10 min	13	10
Mean value ± S D (contractions/10 min)	3 1±1 3	2 7±1 1
Cervical dilatation		
≤2 cm	21	25
>2 cm	13	9
Mean value ± S D (cm)	2 0±0 9	2 0±0 8
Length of pregnancy		
≤30 weeks	7	5
31–33 weeks	18	13
34–36 weeks	9	16
Mean value ± S D (weeks)	32 1±2 2	32 9±2 0

Salbutamol was diluted in 5% dextrose to a concentration of 25 μg/ml The initial dose was 25 μg/min The dosage was thereafter individually adjusted depending on the maternal heart rate or uterine activity within the range 6 25–37 5 μg/min usually between 6 25–12 5 μg/min The treatment was continued for a varying length of time usually between 12 to 24 hours One patient received 160 mg salbutamol over 6 days

Terbutaline was diluted in 5% dextrose to a concentration of 5 μg/ml The initial dose was 5 0–7 5 μg/min The dose was thereafter adjusted depending on the maternal heart rate or uterine activity within the range of 2 5–15 μg/min usually between 2 5–5 0 μg/min The treatment was continued for a varying length of time usually between 12–24 hours In one patient 27 5 mg terbut[...] given over 80 hours

Maternal systolic and diastolic blood pressure [...] and fetal heart rate were registered during the first [...] every 10 min and thereafter at least once every [...]

After cessation of the infusion the treatment was [...]tinued with bed rest and oral administration of salb[...] 2 mg×4 or terbutaline 5 mg×3 respectively

RESULTS

The results obtained are summarized in Table II Delivery within 24 hours occurred in one patient [...] the salbutamol group and in two patients in the terbutaline group A prolongation of the gest[...] for at least one week occurred in the terbut[...] group in 80% of cases and in the salbutamol gr[...] in 74% of cases Most of the patients were deliv[...]ered between the 37th to 39th week of pregn[...] A significant increase in maternal and fetal hea[...] rate was obtained more frequently in the [...]butamol than in the terbutaline group No p[...] developed side effects which necessitated dis[...]tinuance of the treatment The effect on blood pre[...]sure in the doses used was very small Generally [...] small increase in the systolic blood pressure and [...] small decrease in the diastolic blood pres[...] found but the effects were not consistent

No perinatal deaths occurred in the total s[...] groups Among 25 babies with gestational age le[...] than 37 weeks there were only 2 infants wh[...] developed respiratory distress syndrome

le II *Results of treatment*

	Salbutamol		Terbutaline	
	n	%	*n*	%
Number of patients	34		34	
Prolongation of pregnancy				
≥1 week	25	74	27	80
1–7 days	8	23	5	14
<24 hours	1	3	2	6
Mean value (days) ± S D	31 3±22 3		31 1± 0 4	
Gestational age at delivery				
<37 weeks	14	41	12	35
37–39 weeks	15	44	18	53
40–42 weeks	5	15	4	12
Mean value (weeks) ± S D	36 5±3 3		37 2±2 5	
Increase in maternal heart rate ≥40 beats/min	11		8	
Increase in fetal heart rate >20 beats/min or heart frequency >160 beats/min	9		3	

ᵻ III *Results of treatment according to the gestational age and the state of the cervix at the onset of p*

		Prolongation of pregnancy					
		>1 week		1–7 days		<24 hours	
	n	*n*	%	*n*	%	*n*	%
ıan y weeks							
0	12	8	67	4	33	0	0
33	31	_5	81	4	13		6
36	_5	19	6	5	0	1	4
ı al dilatation							
cm	53	48	91	5	9	0	0
cm	15	4	_7	8	53	3	20

r s no difference was found between the sal ımol and terbutaline group with respect to the ı t on uterine activity the groups have been ›ıbıned ın order to analyze the influence of the ‿e of the cervix and the duration of pregnancy at commencement of treatment on the outcome of _*treatment* The results are shown ın Table III duration of pregnancy did not influence the ct of the treatment If cervix was dilated more 1 ? cm the *treatment was successful* (prolonga ı of pregnancy at least one week) ın only 27% ıpared to 91% if cervix was dilated 2 cm or less n 1? patients with ruptured membranes the drugs _lied were able to arrest labour between one and en days ın 7 patients and ın 1 patient the delivery › delayed for 6 weeks

DISCUSSION AND CONCLUSION

present study confirms previous results (7 9) t drugs with more selective β_2 stimulating pro- ties are very effective in arresting premature our without serious adverse side-effects to the ther or infant In the present study no difference effect could be found between the salbutamol and butaline treated group In the salbutamol group a newhat higher incidence of increased fetal heart e was found The explanation might be that the ses used in the two groups are not entirely com *Table* This is also demonstrated by the fact that ly in one patient the initial salbutamol dose of 25 /min was increased whereas in the terbutaline oup the *initial* dose of 5 μg/min was increased in 8 tients

It is a well known fact that the diagnosis prema re labour cannot easily be distinguished from false labour Thus the results of placebo treat ment in different studies vary remarkably 20% (7) 38% (14) and 73% (4) The different results must depend on the selection of the subject and implies that results from different studies are not compar able With the present knowledge of the effect of β stimulating drugs on premature contractions it must however be unethical to perform a study using a placebo group In the present study only patients *with regular contractions at an interval of at least* two per 10 min were included in the study Most of the patients (87%) were delivered before 40 weeks gestation which might indicate that the patients included in the study really were in active labour

In the present study there was no difference in effect between patients of different gestation In a previous study (11) concerning the effect of ethanol on premature labour it was found that ethanol treatment was more effective in patients with a ges tational age of 35–36 weeks (95%) in comparison to 27–32 weeks (67%) The explanation might be that different causes of premature labour are dominant at different gestations *In late pregnancy the* sensitivity of the myometrium to oxytocin is in creased (5) oxytocin released from the neuro- *hypophysis might* therefore be able to induce la bour contractions Oxytocin release can be inhib- ited by administration of ethanol (12) At an earlier gestation other factors contribute to the induction of labour therefore ethanol is less effective in these patients whereas β stimulating adrenergic agents which act directly on the myometrial cell are equally effective at all gestations

As regards the state of the cervix and the out come of pregnancy it is obvious that if cervix is *dilated more than two centimeters the effect of the*

treatment is less reliable Generally only a temporary arrest of labour activity is obtained The results stress the importance of a rapid instigation of treatment to achieve still better results

If the fetal membranes are ruptured the results of treatment with β stimulating agents are rather poor A temporary arrest of uterine activity can however often be obtained

A remarkable observation in the comparative study is that of the 25 infants born before 37 weeks of pregnancy only 2 developed respiratory distress syndrome (RDS) despite no treatment with glucocorticoids having been given to prevent RDS This observation supports recent retrospective studies indicating that the incidence of RDS is greatly reduced in premature infants born of mothers treated with β mimetic drugs (3 8) Experimental studies on fetal rabbits also indicate that β adrenergic agonists may enhance the release of surface active material into the pulmonary alveoli The present study also indicates that treatment with β stimulating agents in the doses used seems to be without risks for the fetus and mother

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THE EFFECT OF BETA RECEPTOR STIMULATING AGENTS ON THE UTERO PLACENTAL BLOOD FLOW

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ract The influence of salbutamol a beta 2 receptor ulating agent on the blood flow through the utero-ental unit was evaluated in the human Serial placenta tigrams were analysed quantitatively after injection 5 mCi Indium 113m by means of a gamma-camera nected on line to a computer The examinations were ormed in the third trimester of pregnancy No seda was used Uterine contractions were not present utamol caused an increase in activity over the placen region corresponding to a 15% increase in blood vol The rise time of the initial phase of isotope accumu m (calculated from 5 to 95% of final activity) was onged by 100% during salbutamol infusion As the rise is proportional to the volume/flow ratio of blood the uteroplacental region our data indicate that utamol infusion causes a decrease in blood flow in the ence of uterine contractions

a receptor stimulating agents have been em yed in obstetrical practice during the last ten rs The efficacy with which these drugs de ase tonus in smooth muscle and arrest uterine tractions is well documented in the literature These properties of the drugs have led to r use in premature labor and in obstetri emergencies (10)

Beta receptor stimulating agents have been re rted to improve fetal condition especially in the ial stage of their administration and secondary to arrest of strong uterine contractions (3) The ugs have also been found of value for the treat ent of fetal asphyxia (13) Little information is ailable however regarding their effect on pla ntal blood flow and fetal oxygenation In the egnant ewe isoproterenol has been reported to in ease uterine blood flow in spite of a decrease in rfusion pressure (8) More recently contrary results have been obtained in studies using other synthetic beta receptor stimulating drugs (4) Studies in sub-human primates have shown moreover that the administration of isoproterenol to the sedated mother leads to a reduction of the arterial oxygen tension in the intrauterine fetus the fetal arterial PO_2 being taken as an indicator of the perfusion of the intervillous space (7)

The aim of this investigation has been to study the influence of beta receptor stimulating agents on the blood flow through the placenta in the human Scintigraphic techniques were chosen and two modifications have been employed in determining the amount of radioactivity over the placental site following intravenous injection of ^{113m}Indium-chloride during basic conditions and during the administration of salbutamol

MATERIAL AND METHODS

Sixteen pregnant women in the last trimester of pregnancy referred for scintigraphic localization of the placenta because of clinical suspi ion of placenta previa were asked to participate in this investigation authorized by the local ethical committee Determination at steady state of the radioactivity over the placental site was performed in 11 women and the initial phase of accumulation of radioactivity was determined in another five For this purpose we used ^{3m}In which following its intravenous injection is bound almost completely to transferrin and only a negligible amount of activity (less than 0 5%) will pass the placental barrier to the fetus The fetal radiation dose is only about 10 mrad per mCi given to the mother (5)

Determination at steady state of isotope uptake over the placental site was performed using a gamma-camera with diverging collimator on line with a computer positioned in a frontal view over the placenta Serial

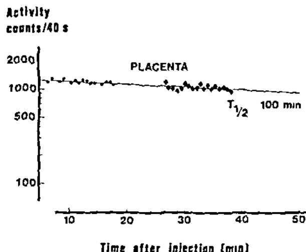


Fig 1 Time function of activity in placenta after injection of ^{113m}In (subject MU)

tigrams were recorded in image matrices of 64×64 elements corresponding to a geometric resolution of about 5 mm The measurement started a minimum of 5 min after the intravenous injection of 1 mCi of ^{113m}In thereby ensuring that the isotope and blood were homogeneously mixed before recording The sampling time of each scintigram was 40 s and the total recording time 12 min By computerized summation of the scintigrams a detailed image was obtained in which the placenta could be identified with accuracy and outlined for subsequent analysis of the time activity distribution

Five of the 11 women received an intravenous infusion of salbutamol in a dose of 15 μg/min beginning after the completion of the recording of basic conditions The radioactivity over the placental site was then recorded again at 40 s intervals during another 12 min This recording started 5–7 min after the commencement of the salbutamol administration Six women who did not receive salbutamol were examined during a similar additional recording period for control purposes

Determination of initial phase of isotope accumulation over the placental site was performed in 5 women These measurements were performed using a 50×50 mm NaI (Tl) detector with a conic collimator (length 190 mm front opening 90 mm) positioned over the placenta previously localized by ultrasonography The detector was connected to a time scaling multi-channel analyser The recordings started in direct connection with the intravenous injection of 0 5 mCi ^{113m}In The radioactivity was determined during 9 s periods for 6 min Each patient was examined on two separate occasions first during basic conditions and second during the i v infusion of salbutamol in a dose of 15 μg/min The administration of salbutamol was always started 15 min before the isotope injection This latter detector system was preferred for the measurement of radioactivity accumulation as it is more sensitive than the gamma-camera The duration of sampling times could then be minimized (9 s) without losing satisfactory statistical precision during the initial steep part of the time activity curve

The continuous recording of arterial blood pressure and the withdrawal of blood samples at intervals for analysis of acid base parameters were facilitated by use of an intraarterial catheter inserted transcutaneously into the brachial artery of the mother before the commencement of the examinations The blood pressure was recorded on an ink jet recorder via an inductance pressure transducer connected to this catheter

RESULTS

Determination at steady state of isotope activity over the placental site When the individual number of counts per 40 s period had been plotted along the y axis in a semilogarithmic diagram against time along the *x* axis all values could be adapted to a line with a slope representing the physical half time of ^{113m}In The values during the second period of determination in the women who did not receive salbutamol were in all instances positioned along the continuation of the line representing the decay of the isotope which was found during the first period of determination in the same individual (Fig 1) The observations during infusion of salbutamol however followed a line which was displaced 1 times towards higher activity values but parallel with the line reflecting basic conditions (Fig 2)

Values from 18 points of the first 12 min period of measurement were then added and compared with the sum of the values from 18 points of the second period after correction for the physical decay In Table I the results of these two time periods are given for each control patient There were

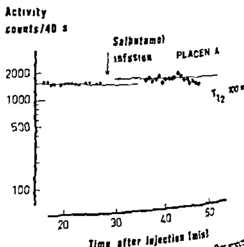
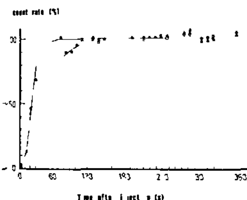


Fig 2 Time function of activity in placenta after injection of ^{113m}In before (filled circles) and during (filled circles) salbutamol infusion (subject MN)



1 Time function of initial accumulation of ^{113m}In in nta without (filled triangles) and with (open circles) ion of 15 μg/min salbutamol (subject BP) The curves lized to 100% at their respective maximum s

ificant changes during these two periods the of uptake between the first and the second od being equal to one When salbutamol was l the infusion was given before the second od and it led to an increase in the uptake of ope in the placental region by an average of equivalent to a 15% increase in blood volume ble II)

etermination of initial phase of isotope accumu on over the placental site The maximum activ egistered in each patient was taken as 100% and d for the normalization of values during the ini part of the curve It was observed that the umulation of activity over the placental region considerably slower during the administration albutamol than during basic conditions The rise defined as the time for increase of activity

ble I *Registration of* ^{113m}*In steady state uptake lacenta in control patients*

	Uptake in placenta (counts)		
	First period	Second period	Ratio of uptake between second and first period
l	20 ?×10³	19 8×10³	0 98
	17 9×10³	21 4×10³	1 19
	15 9×10³	17 0×10³	1 07
1	25 0×10³	24 4×10³	0 98
	27 8×10³	30 4×10³	1 09
	8 3×10³	27 7×10³	0 98
an			1 05±0 09 (1 S D)

Table II *Effect of salbutamol infusion on the* ^{113m}*In steady state uptake in placenta*

	Uptake in placenta (counts)		
Subject	Reference period (first period)	Salbutamol infusion (second period)	Ratio of uptake with and without salbutamol
MN	23 6×10³	27 1×10³	1 15
IK	_ 4×10³	26 1×10³	1 17
KN	24 9×10³	26 6×10³	1 07
LN	41 9×10³	48 7×10³	1 17
EM	40 0×10³	46 7×10³	1 17
Mean			1 15±0 05 (1 S D)

from 5–95% of the maximum count rate was prolonged 100% The results are given in Table III and depicted in Fig 3

Arterial blood pressures were normal in all patients Only small changes in arterial pressures were recorded during salbutamol infusion (Fig 4) On average there was a slight increase in the systolic pressure while the mean and diastolic pressures were essentially unchanged Concomitantly a progressive increase in *heart rate* was registered during the first 15 min of infusion of salbutamol At the end of the infusion period heart rate had increased 40% and the women invariably felt palpitation and tremor *The arterial tensions of O and* CO_2 and the *pH* values were within the normal range and were not significantly influenced by the infusion of salbutamol

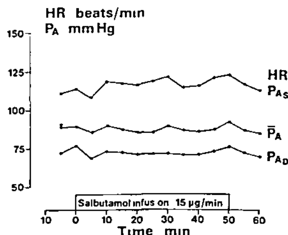


Fig 4 Arterial blood pressure (*P* systolic mean diastolic) and heart rate (*HR*) during salbutamol infusion

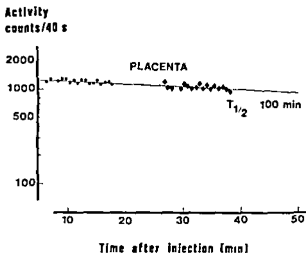


Fig 1 Time function of activity in placenta after injection of ^{113m}In (subject MU)

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Five of the 11 women received an intravenous infusion of salbutamol in a dose of 15 μg/min beginning after the completion of the recording of basic conditions The radioactivity over the placental site was then recorded again at 40 s intervals during another 12 min This recording started 5–7 min after the commencement of the albutamol administration Six women who did not receive salbutamol were examined during a similar additional recording period for control purposes

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The continuous recording of arterial blood pressure ... *the withdrawal of blood samples at interval* ... *analysis of acid base parameters* were facilitated ... use of an intraarterial catheter inserted transcu... into the brachial artery of the mother before the commencement of the examinations The blood pressure ... recorded on an ink jet recorder via an inductance ... transducer connected to this catheter

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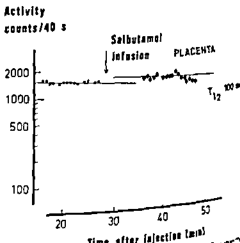


Fig 2 Time function of activity in placenta after ... of ^{113m}In before (filled circles) and during (filled ... salbutamol infusion (subject MN)

cular beds in the somatic vessels would be to divert blood away from the uterine circula -Reflexly mediated regional vasoconstriction a resultant reduction in conductance not l to any specific change in mean arterial pres might also occur (11) The increased rise time tope accumulation and the decrease in blood over the placental region found in this study be secondary phenomena induced by these mechanisms Furthermore isoproterenol es the placenta readily and might cause a re bution of fetal blood flow with a diversion of ight ventricular output of the fetus from the sion of the placenta as a result More detailed s with refined techniques are needed in or to increase our knowledge regarding the nacologic effects of various beta receptor ilating drugs during pregnancy

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THE INFLUENCE OF PRESSURE UPON THE FETAL HEAD DURING LABOUR

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act In contracted pelvis moulding of the skull is caused by the force of the amniotic fluid pressure he resistance of the pelvis In normal labour and mal uterine action the moulding of the skull bones is d by the head to cervix pressure as has been demon d by intra uterine tokometry By contrast in the acted pelvis there are no mouldings between the two tal bones In breech presentation during the first of labour the moulding of the skull bones is ex ed by the differing resistance of the various skull s against the amniotic fluid pressure

matic lesions of the fetus caused by various sures are seen at operations such as extraction e fetus in vertex as well as in breech presenta

The fetal head in particular is affected by ous pressures which cause moulding of the skull s and fractures are sometimes seen The ldings may cause rupture of the tentorium and bral hemorrhage In a conservatively treated erial from Sabbatsbergs hospital 1949–1959 prising 23836 infants 647 died perinatally Of infants 17 3% showed rupture of tentorium dgren et al 1962) By active obstetric man ment the risk has been reduced but we do not w how many children survived who had cere l palsy or mental retardation caused by these ssures

Mouldings occur as a result of contracted pelvis also in cases of normal labour abnormal uterine ion secondary inertia and in breech presenta n In the latter cases the mouldings are caused by various intra uterine pressures and the in ased resistance of the pelvic floor The purpose this paper is to demonstrate the various types of uldings and the different pressure conditions ich cause these mouldings

METHOD

In collaboration with Ingelman Sundberg & Ljungström (5) the method of intra uterine tokometry was worked out by using strain gauges By using this method we have been able to study the biomechanics of the cervix in labour (6 7 8)

The X ray pictures have been made by Ingmar Fernstrom M D Karolinska sjukhuset Stockholm

Normal labour

By using the method of intra uterine tokometry we found that during contractions in vertex presentation the head to cervix pressure is on average three to four times higher

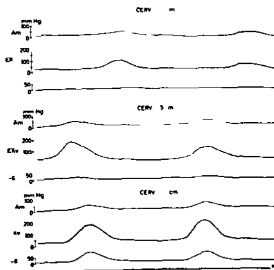


Fig 1 Recordings of the intra uterine pressures during the first stage of normal labour *Am* Amniotic fluid pressure *Ekv* head to cervix pressure at the equator of the fetal head −6 head to cervix pressure 6 cm below the equator of the fetal head The head to cervix pressure at the equator increases during the progress of the first stage because of the increased amniotic fluid pressure

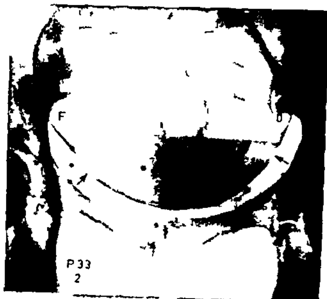




Fig 2 Mouldings of the skull bones in early first stage of normal labour *S* Symphysis *P* promontorium *PR* and *PL* parietal bones *F* frontal bone *O* occipital bone Note the mouldings at the arrows





Fig 3 Mouldings of the skull bones in late first stage of normal labour *S* Symphysis *P* promontorium *PR* and *PL* parietal bones *F* frontal bone *O* occipital bone The moulding has increased Same patient as in Fig 2

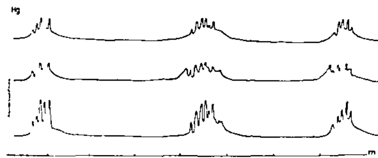


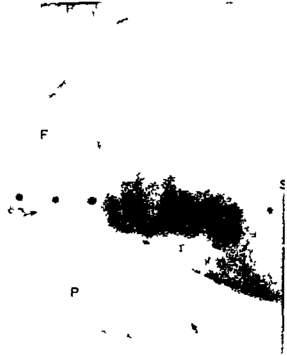
Fig 4 Recordings by using intra uterine tokometry in second stage of labour *Am* Amniotic fluid pressure *Eh* head to cervix pressure at the equator of the fetal head −3 Head to cervix pressure 3 cm below the equator of the fetal head Note the higher pressure in the level −3 coresponding to the resistance of the pelvic floor

the corresponding amniotic fluid pressure The ...aneous recorded head to cervix pressure decreases ...ds the lower pool of the fetal head During the first ...of labour the head to cervix pressure at the equator ... fetal head is on average the same at the same ...tic fluid pressure throughout the first stage except ...upture of the membranes when the head to cervix ...ure at the equator increases and the pressures at ...levels decrease As the amniotic fluid pressure in...es during the progress of the first stage of labour the ...to cervix pressure at the equator of the fetal head ...creases (Fig 1)

The high head to cervix pressure at the equator causes a moulding of the skull bones (Fig 2) The parietal bones are elevated in relation to the frontal and occipital bones giving a level difference in the coronal and lambdoid sutures This moulding increases during the progress of labour (Fig 3) corresponding to the increased head to cervix pressure at the equator of the fetal head and the prolonged time of the prevailing increased pressures

During the second stage of labour the head to cervix pressure at the equator decreases (Fig 4) and the moulding of the head likewise (Fig 5) The head to cervix pressure at lower levels increases because of the high





...5 Fetal head during the second stage of normal ...our *S* Symphysis *P* promontorium *PR* and *PL* parietal bones *F* frontal bone *O* occipital bone Note the remoulding of the skull bones

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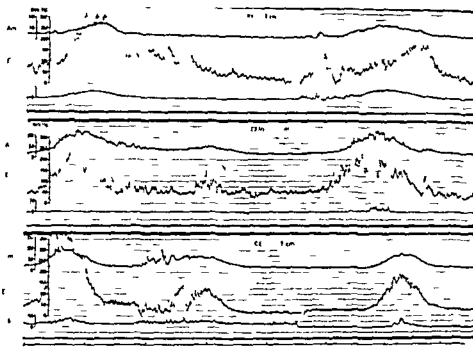


Fig 6 Recordings of the intra uterine pressures in spastic uterus *Am* Amniotic fluid pressure *Eh* head to cervix pressure at the equator of the fetal head −6 head to cervix pressure 6 cm below the equator of the fetal head Note the high head to cervix pressure at the e caused by spastic contractions appearing as a ... pattern added to the pressure curves



Fig 7 Mouldings of the skull bones in spastic uterus *P* Parietal bone *F* frontal bone *O* occipital bone Note the large moulding between the occipital and parietal bones

Fig 8 Mouldings of the skull bones in breech presentation Note the impression of the parietal bone at the arrow (↓)

istance of the pelvic floor The latter may cause rupture he ter orium especially in primigravidae but the risk be redu ed by pudendal block anaesthesia and siotomy

normal ute ine action

some cases of hypertonic inertia spastic contractions ur in the annular musculature of the lower part of the pus (Fig 6) The head to cervix pressure increases and mo lding likewise (Fig 7) The moulding is otherwise the same type as in normal labour The dislocation of skull bones can be large—up to 25 mm in this type of pertonic inertia In a material of 56 such patients all mitored and selected among women with violent con actions 16 or (29 %) of the infants died all due to pture of the tentorium In such cases caesarean section ght to be done as soon as the diagnosis has been veri d

Cervical rigidity may cause an increased head to cervix pressure but can be successfully treated by the vibration method

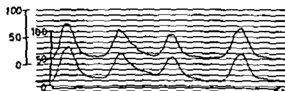


Fig 9 Amniotic fluid pressure recorded by two strain gauges in breech presentation The upper curve shows the measurement in the middle part of the uterine cavity the lower curve the pressure between the fundus and the fetal head

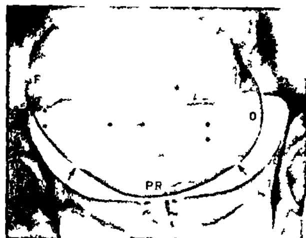




Fig 10 Contracted pelvis of the inlet *S* Symphysis *P* promontorium *PR* and *PL* parietal bones *F* frontal bone *O* occipital bone Note the moulding be [illegible] parietal bones

Breech presentation

The risk of rupture of the tentorium of the fetus at vaginal delivery is rather high in breech presentation—higher than in vertex presentation In the material referred above rupture of the tentorium was seen in 27% of the infants who died perinatally in comparison with 15% in vertex presentation

During the first stage the pressure of the amniotic fluid on the fetal head is less than that of the head on the cervix in vertex presentation and likewise also the moulding (Fig 8) The pressure is the same on the various skull bones (Fig 9) but their resistance to the increased [illegible] pressure differs during contractions which explains [illegible] moulding The risk of rupture of the tentorium is [illegible]

During the second stage the fetal head passes the [illegible] canal quite rapidly and with the fronto-occipital [illegible] ference perpendicular to the direction of fetal [illegible] but on the contrary to be compared with the [illegible] bregmatic circumference in vertex presentation [illegible] larger the pelvis the wider must the birth canal be [illegible] to avoid injury to the fetal head

However the increased risk of lesions to the fetal [illegible]



Fig 11 Contracted pelvis of the outlet *S* Symphysis *P* promontorium *SP* spines *PR* and *PL* parietal bones *F* frontal bone *O* occipital bone Note the moulding between the parietal bones but also between other skull bones

eech presentation is not only explained by the in fled risk of contracted pelvis The cervical dilatation is trolled by two main factors—the wedge effect of the nting part of the fetus and the brachystasis of the le cells of the corpus The circumference of the rump aller than that of the fetal head and still smaller when et are presented When the cervix is dilated for the ge of the rump the wedge effect is no longer acting the cervical dilatation depends on the mechanism of brachystasis of the muscle cells of the corpus *only* h takes longer time Extraction of the fetus in this of labour increases the risk of rupture of the num and it is important to adopt a wait and see poli

acted pelvis

ontracted pelvis special mouldings are seen Fig 10 vs the moulding caused by narrow inlet In normal ur the moulding caused by the cervix elevates both tal bones in the same degree but in contracted pelvis one bone is elevated giving a level difference in the tal suture Fig 11 shows the level difference between parietal bones but also between other skull bones in a of narrow outlet which also are seen in narrow inlet one tries to deliver the patient by vacuum extraction moulding increases and the risk of brain lesions of the s increases By using forceps the risk of brain lesions e fetus is less but the delayed operation may increase risk of fetal distress and the risk of lesions of the her increases Therefore the method to choose is sarean section in cases of contracted pelvis

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LATE SEQUELAE OF INDUCED ABORTION IN PRIMIGRAVIDAE

The Outcome of the Subsequent Pregnancies

Oddmund Koller and Siri Nome Eikhom

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ract In a retrospective study a group of 137 women legal abortion in their first pregnancy was compared a group of 133 women with spontaneous abortion re 8 weeks) and a group of 1 9 women who had a ery (beyond .8 weeks) in their first pregnancy Three s of ectopic pregnancy were recorded in the second nancy in the legal abortion group none in the other ps The delivery group showed the best reproductive ormance while the spontaneous abortion group had highest frequency of early abortion and the induced tion group the highest frequency of late spontaneous tion and premature delivery and in addition a trend ards earlier spontaneous onset of labour in their sec pregnancy There was a conspicuous decline of the oductive performance in the third and fourth preg y of the induced abortion group and a highly sig ant increase of the rate of late abortion compared the overall rate of late abortion in the department induced abortion group showed an increased rate spontaneous primary and premature rupture of the nbranes and also a definite trend towards lower weight e newborn especially beyond 41 weeks of pregnancy re was a close correlation between induced abortion in s below 17 years of age on the one hand and repeated rtion and/or unmarried state in the second pregnancy the other A significant correlation was revealed be en early menarche and legal abortion in the first preg cy and also between early menarche and unmarried e in the first pregnancy as found in a random series of first pregnant women

rly complications of induced abortion are roughly analysed in the medical literature but re are relatively few publications dealing with more important aspect of late sequelae This is a grettable situation especially because a large and reasing number of young women have their first egnancy terminated by induced abortion Harm l effects on later reproductive performance are of eater importance for this category of women than r those who already have a family

One of the main reasons for the conspicuous scarcity of follow up reports on subsequent preg nancies in women who have had their first preg nancy terminate probably is the risk that a pro- spective follow up procedure might be emotionally very disturbing and create a great deal of unhappi ness among the women concerned

The present study is retrospective and based on hospital records In some areas incomplete informa tion had to be accepted in order to maintain the strictest secrecy

MATERIAL AND METHODS

The report is based on the record of the obstetrical de partment of a combined regional and university clinic where admittance is accepted for geographical as well as medical reasons For this reason the results in the study group cannot be compared with the general data from the Norwegian Medical Birth Registry

Statistically reliable groups must be provided from the clinic in question A study group and 2 control groups were established The number of cases in the groups is not the same because cases with multiple pregnancy and non-obstetrical diseases were excluded after collection of the material

Group I comprises 137 women the total number of women admitted as pregnant from 1972 to November 15th 1974 who according to their records had had legal abor tion of their first preenancy Of the 137 induced abortions of the first pregnancy 96 were performed at our depart ment 31 at other Norwegian hospitals and 10 abroad (U K) Detail of the operation in these last 41 cases were missing but there were no indications of major complica tions The methods of abortion in our department in the presented cases were D & C vacuum aspiration and intra amniotic hypertonic saline It appears that a curettage was always used as a final step of a suction procedure in order to make sure that no produ ts were retained Dilatation of the cervix in one step was only performed below 10 weeks of pregnan y In more advanced pregnancies gradual dila-

Table I

	Group I	Group II	Group III
Age at first pregnancy	19 5±3 4 (15–33)	23 4±3 9 (16–33)	23 7±3 4 [illegible]
Age at second pregnancy	22 2±4 2 (16–40)	25 ?±4 1 (17–35)	[illegible]
Not married at second pregnancy	*36/137 (26 3%)*	*5/133 (3 8%)*	2/129 [illegible]
Number of cases where the age at menarche is known	129/137 (94 2%)	128/133 (96 2%)	125/129 (96 9 [illegible]
Number of cases with early menarche (before 13 years of age)	41/129 (31 8%)	50/128 (39 1%)	[illegible]

tation was achieved over 12–14 hours with Lovset s dilatator an instrument with two steel branches gently opened by continuous traction by a metal string in such a way that the cervical opening is never blocked as with the use of laminaria

Group II comprises 133 women collected at random from the same period with a record of spontaneous abortion before 28 weeks in their first pregnancy

Group III comprises 129 women collected at random from the same period with a record of delivery after 28 weeks or more in their first pregnancy

The statistical methods have been Yates corrected Chi square Fisher s exact probability tests and Wilcoxon s test for two samples (two tailed)

RESULTS

The characteristics of the groups and the outcome of the second pregnancy are compared Then the outcome of the third and fourth pregnancy in the study group is presented and some trends compared with those of the total material of the department

Data on *age married state and menarche* are given in Table I *The mean age* of the women in the study group was 4 years below that of the other groups This is undoubtedly related to the fact that young age represents one of the indications for legal abortion

There is a significantly (p<0 001) higher percentage of women in the study group who were unmarried at their second pregnancy compared with each of the other groups The findings indicate a relatively low degree of social adjustment as far as married state is concerned in the women who had their first pregnancy terminated by legal abortion This is especially true for those who have had their pregnancies terminated before they were [illegible] years of age They comprise a far greater part of the unmarried than the married women in the study group (p=0 008)

Relatively early sexual maturation indicated by menarche before 13 years of age was more frequently found in the study group than in group III (p=0 03) Group II had the highest frequency but not significantly different from the study group This means that both groups of women who had suffered abortion in their first pregnancy had had relatively early sexual maturation

That early menarche predisposes to an unwanted pregnancy is rather self evident An unwanted pregnancy

Table II

Number with primary spontaneous rupture of the membranes within parentheses

	Groups			Total number
Outcome of the second pregnancy	I	II	III	
Legal abortion	7	0	6	13
Ectopic pregnancy	3	0	0	3
Early spontaneous abortions (below 14 weeks)	6	16	[illegible]	24
Late spontaneous abortions (14–21 weeks)	2 (1)	0	0	[illegible]
Premature delivery (birth weight 500–2 499 g)	10[a] (8)	7 (1)	3 (0)	20
Birth weight 2 500 or more	109	110	118	337
Total number	137	133	129	399

1 case where the relation between rupture of the membranes and onset of contractions are unknown

[a] 1 induced case

3 induced cases

e III *Interval in hours between spontaneous ~ure of the membranes and onset of the contrac*

–

val urs	Groups I	II	III	Total number
	10	13	19	42
1	10	6	3	19
more	9	3	0	12
l number	29	2	22	73
l number of cases orded	97	90	10?	289

'y may be terminated as in the study group may also be allowed to continue and then often an unmarried mother In a random series of first pregnancies in our obstetric department y menarche was found in 20 of 45 unmarried nen i e 44 4% against 57 of 205 married women ?7 8% a difference which is statistically sig cant (p=0 03)

he outcome of the second pregnancy in the 3 ıps is shown in Table II

even of the women in the study group had also r second pregnancy terminated by *legal abor* Five of these women were 16 years or younger he first abortion Even if ectopic pregnancy and y abortion are excluded there was a signifi tly higher proportion (p=0 007) of very young s among those who has legal abortion in their ond pregnancy than among those who accepted ır second pregnancy

ecause the study group only comprises women o had become pregnant again nothing can be l about the *infertility* rate after legal abortion

The series however contains one case who had had an induced abortion which was uncomplicated except for fever without local symptoms on the first postoperative day She married 3 years later and proved to be infertile because of bilateral tubal oc clusion A plastic operation was performed on the tubes and five years later she had an *ectopic preg nancy* In this case the induced abortion was probably the primary cause of the events leading to this complication Ectopic pregnancy occurred other wise twice in the study group 2 and 3 years re spectively after the induced abortion One of these abortions was also complicated by fever with out local symptoms on the first postoperative day This indicates that fever without local symptoms might be of more importance than generally con sidered

The overall rate of ectopic pregnancy in the first pregnancy at the department for the period 1967–71 was 41/8765 i e 0 42% If all 3 cases are accepted as a result of induced abortion the difference is significant (p=0 03)

Early spontaneous abortion (before 14 completed weeks of pregnancy) occurred significantly more frequently in group II where the women already had had a spontaneous abortion than in the other groups compared with the study group and the delivery group p=0 03 and 0 001 respectively

Late spontaneous abortion (from 14 to 21 com pleted weeks or fetal weight of less than 500 g) occurred only in the study group In group II how ever one case had been treated prophylactically with cervical suture because of suspected cervical incompetence and labour started immediately after the removal of the suture at term In this case late abortion or premature delivery might have occurred if the woman had not been treated

ble IV *The outcome of the second third and fourth pregnancy after induced abortion in the first gnancy*

r cent in parentheses

gnancy	Ectopic	Induced abortion	Early abortion	Late abortion	Premature delivery	Mature delivery	Total number
	3 (? ?)	7 (5 1)	6 (4 4)	? (1 5)	10 (7 3)	109 (79 6)	137 (100 0)
	0	5 (10 0)	4 (8 0)	5 (10 0)	5 (10 0)	31 (6? 0)	?0 (100 0)
	0	1 (6 3)	? (12 5)	? (1? 5)	(1_ 5)	9 (56 3)	16 (100 0)
tal number	3 (1.5)	13 (6 4)	13 (6 4)	9 (4 4)	17 (8 4)	149 (73 4)	?03 (100 0)

Birth weight 500–? 499 g

Table V *Consecutive induced abortions*

	First pregnancy				Second pregnancy				
	Age	Married	Weeks of pregnancy	Complications	Interval (months)	Age	Married	Weeks of pregnancy	Complications
1	16	No	7–8	None	5	17	No	1?	None
2	15	No	?	?	9	16	No	?	?
3	19	No	7–8	None	7	20	No	?	?
4	16	No	12	None	12	18	No	1?	None
5	16	No	11–12	None	11	17	No	10–11	None
6	20	No	11	None	5	21	No	8–10	None
7	16	No	11	Bleeding Repeated curettage	5	17	No	?	?

Premature delivery (birth weight 500–2 499 g) Only in the study group was there 1 case between 500 and 1 000 g One case in the study group and 3 cases in group II were induced because of severe preeclampsia If these cases in addition to the cases with induced abortion and ectopic pregnancy are *excluded* there is a significantly higher rate of late spontaneous abortion and premature delivery combined in the study group than in the other groups combined ($p=0\ 002$)

Duration of pregnancy more than 40 weeks was [illegible]nificantly less frequent in the study group where [a]lso the induction rate was lower than in the two other groups combined ($p=0\ 006$) This indicates a trend towards earlier spontaneous onset of labour

If a cervical lesion is the factor responsible for this trend and for the increased frequency of late spontaneous abortion and premature delivery one would expect a higher rate of primary as well as premature rupture of the membranes (Table III)

Primary rupture of the membranes defined as an interval of 6 hours or more between this event and onset of labour pains was more frequent in the study group than in each of the other groups Compared with group III the difference was highly significant ($p<0\ 001$) but did not reach the level of significance for group II ($p<0\ 10$) Late abortion and premature delivery started more often with primary spontaneous rupture of the memb[illegible] in the study group than in the other groups combined ($p=0\ 01$) See Table II

Incompetent cervix however may not be the only responsible factor This was indicated by a case in the study group who after a late spontaneous abortion in the second pregnancy was treated prophylactically with a cervical suture in the third pregnancy The outcome was nevertheless a prem[illegible] baby

The duration of labour after starting of the contractions was very similar in the groups of women who had had an abortion in their first pregnancy *The women who had passed 28 weeks of pregnancy however* had a highly significant shorter duration of labour ($p<0\ 001$)

The weight of the newborn after 36 weeks of pregnancy was significantly lower ($p<0\ 05$) in the study group than in the other groups and [illegible] *tively rarely reach* 3 500 g ($p<0\ 001$) The [illegible] *was analysed separately for each week of pregnancy* and it turned out that except for [illegible] week the difference was mainly c[illegible]used [illegible] significant difference after 41 weeks of pregnancy Group I/group II $p<0\ 005$ and group I/group III $p<0\ 01$ The findings seem [illegible] growth limitation than an early starting [illegible] tardation Intrauterine adhesions or other [illegible] logical [illegible]esses limiting the capacity of the [illegible] [illegible] occur after an induced abortion

gnancy			Fourth pregnancy		
ar ed	Outcome of preg nancy		Age	Mar ried	Outcome of preg nancy
es	Late spont abortion 16 weeks		?2	Yes	Stillbirth 40 weeks 1 450 g
o	Late abortion 18 weeks				
es	Full term 3 ?40 g				
lo	Full term 3 180 g				
lo	Full term 3 160 g				
'es	Full term 3 3 0 g				
lo	Criminal abortion Bleeding Infection		21	Yes	Full term 3 480 g

ao cases of *immunization* one of Rh and one e type occurred in the study group none in the r groups

te perinatal mortality was highest in the ntaneous abortion group but there was no ficant difference between the 3 groups Only of the prematurely delivered babies in the study p died but because many of them had a very birth weight later sequelae may occur

he outcome of the total number of pregnancies rded after induced abortion of the first preg y is given in Table IV

epeated induced abortions were of two types secutive and intermittent with one or two in ening pregnancies

survey of the *consecutive induced abortions* is n in Table V

ive of the seven cases were 16 years or younger he first abortion as stated above Cases 1 and 2 h suffered late spontaneous abortion in the third gnancy while the fourth pregnancy in case 1 had articularly unhappy outcome a stillborn small dates fetus She was a highly nervous type and s treated with sedatives Case 7 illustrates that n ? legal abortions and one complicated criminal ortion are not incompatible with a happy out ne of a fourth pregnancy

In addition there are 6 induced abortions of the *ermittent* type They had had their first abortion from 16 to 20 years of age mean age 17 8±1 5 i e at an earlier age than the average in the study group

These findings indicate that women with induced abortions at an early age represent a high risk group for unwanted pregnancies Both social problems and especial vulnerability of young girls to the men tal trauma of induced abortion may be responsible for this

Table IV shows a gradual rising rate of both *early* and *late spontaneous abortion* as well as *premature delivery* from the second to the fourth pregnancy

The cases with *late spontaneous* abortion (14–21 weeks of pregnancy) were all treated at our depart ment and the frequency in the study group conse quently can be compared with the overall frequen cy Table VI shows a highly significant increased rate of late abortion in the study group The table also shows a gradual rising of the rate in the total material A rising rate of late abortion is therefore not a specific trend for the study group as shown in Table IV Both increasing age and trauma of the reproductive tract may be responsible

Characteristics in the study group with possible relation to late abortion and premature delivery

The age of the woman at the abortion More of the women who suffered late abortion or premature delivery had had their first pregnancy terminated before the age of 18 than those with full term deliv ery (birthweight 2 500 g or more) The difference however was not statistically significant ($0 1 > p > 0 005$)

Duration of pregnancy at the time of abortion was unknown in 41 cases Compared to the general distribution of duration in the 96 abortions performed in our department the patients who sub-sequently suffered late abortion or premature deliv ery had a more favourable distribution with nearly doubled frequency of early pregnancies of 8 weeks duration or less

Early complication rate in the study group was 13 5% and in those of the group who later suffered late abortion or premature delivery 2/18 i e 11 1% Uncomplicated induced abortion represents evi dently no guarantee against complications in a later pregnancy

The details of the abortion techniques were un known in as many as 41 cases The material is therefore poorly suitable for an analysis of the significance of the abortion procedure We did

Table VI *Late abortion (14–21 completed weeks)*

Number and rate as to number of pregnancies (induced abortions early abortions and ectopic pregnancies excluded) Per cent in parentheses

Group I	Over all occurrence at the department 1967–1971	Statistical difference
2/121 (1 65) Second pregnancy	5/8765 (0 057) Recorded as first pregnancy	$p<0\ 002$
5/41 (12 20) Third pregnancy	9/5592 (0 161) Recorded as second pregnancy	$p<0\ 001$
4/13 (30 77) Fourth pregnancy	13/5977 (0 218) Recorded as third pregnancy	$p<0\ 001$

Number of cases with previous induced abortion ectopic pregnancy and early abortion are not recorded

however not expect to find a tendency to an inverse correlation between the duration of the pregnancy at the time of abortion and also the rate of early complication on one hand and later sequelae in the subsequent pregnancies on the other The operation procedures were therefore more closely examined especially the degree of dilatation of the cervix It was found that this had exceeded 10 mm in the large majority of cases Even if the abortions appeared to be uncomplicated the cervical canal may have been damaged

Two of the three women in the study group whose second pregnancy was extrauterine had fever without local symptoms on the first postoperative day This type of complication may be [illegible]ore important than is generally considered

DISCUSSION

An association between induced abortion and ectopic pregnancy has been suggested in several reports and confirmed in a case control approach (6) The finding of 3 cases of ectopic pregnancy in the legal abortion group fits with this hypothesis Considering the unquestionable risk of infection connected with induced abortion no wonder that an ectopic pregnancy occasionally may be caused by this operation Two of the three patients had fever without local symptoms on the first postoperative day

The results confirm previous publications reporting of an increased rate of late abortion and premature delivery (5 7 8) and also a trend towards earlier onset of labour (5 7) in the second [illegible] nancy after legal abortion of the first

It is accepted as a general trend in reproduc[illegible] performance that the prognosis is better for the second delivery than the first and then grad[illegible] poorer with increasing number of deliveries Th[illegible] general trend does not hold for the wom[illegible] were legally terminated in their first pregnan[illegible] shown in Table IV there is a conspicuous decl[illegible] the reproductive performance in the third [illegible] fourth pregnancy a long time effect that as [illegible] we know has not been demonstrated before Th[illegible] findings of a significantly increased and incre[illegible] rate of late abortion indicate that the terminat[illegible] the first pregnancy had represented a major tra[illegible]

The trend towards earlier spontaneous onse[illegible] labour premature delivery and late abortion ma[illegible] caused by similar mechanism or mechanisms Se[illegible] eral observations indicate that cervical [illegible] tence may play a part in the pathogenesis (1[illegible] Increased rate of primary and premat[illegible] the membranes has been demonstrated in [illegible] present study and also by Lembrych (5) Th[illegible] strengthens the hypothesis of a cervical lesion [illegible] has however been observed that cervical [illegible] does not always prevent early onset of labour

In the present study the weight of the newb[illegible] in the study group proved to be relatively l[illegible] compared with the control groups and espec[illegible] for pregnancies of more than 41 weeks durat[illegible] addition there is an example of severe growth [illegible] dation in the fourth pregnancy where the wo[illegible] had had two consecutive abortions (Table [illegible] These findings seem to indicate that not o[illegible] cervical but also a corporal lesion may contr[illegible] to the reproductive failures Induced abortion [illegible] type of operation that may predispose to [illegible] adhesions (4) The possibility of a partial thr[illegible] sis of the uterine vessels caused by the sud[illegible] terruption of a rapidly developing utero-plac[illegible] circulation must also be kept in mind

One of the girls with repeated abortions who [illegible] a particularly unhappy reproductive history [illegible] suffered from a severe neurosis said to [illegible] appeared after the first abortion Bahn[illegible] Bjerkedahl (1) found that women with neur[illegible] often experience reproductive complications [illegible] failures A multifactorial etiology in repro[illegible] failure is probably often at play

In this relatively small material the increased [illegible] of late reproductive sequelae in the very [illegible]

its did not reach statistical significance The however has revealed a close correlation ..en induced abortion in girls below 17 years of ..n the one hand and repeated induced abortion .. ll as unmarried state in the second pregnancy ..e other These girls comprise undoubtedly a ..isk group for unwanted pregnancies

results from the present study strongly indi ..hat induced abortion in primigravidae espe .. the very young ones is far from an innoxious ..dure It remains to be proved that new techni ..can make it safer The psychological trauma is ..y rate inevitable and prophylactic measures to ..e the frequency of unwanted pregnancies ..ally at an early age are highly desirable

..e present study has revealed a significant cor ..on between early menarche on the one hand ..nduced abortion as well as unmarried state in ..rst pregnancy on the other A significant cor ..on between pregnancy before 15 years of ..and early menarche was demonstrated by ..hoelter et al (2) That early sexual maturation ..ases the risk of unwanted pregnancy is also ..r self evident and girls with early menarche ..ld be considered a high risk group in this re ..t.

.. explanation can be offered for the finding that ..menarche also was correlated with spontane ..bortion in the first pregnancy

..ere was a non significant trend towards nega ..correlation between duration of the pregnancy ..e time of termination as well as complication rate on the one hand and late abortion or premature delivery on the other Cervical dilatation of more than 10 mm may be responsible for this (3)

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MATERNAL DEATHS IN ICELAND 1911–1975

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act Death certificates for all deaths in Iceland are able since 1911 In this report on maternal deaths all n who died after the 28th week of pregnancy during ry and during the first eight weeks after delivery are ded irrespective of the cause of death Out of 225 891 en who delivered during the 65 year period 371 en died Maternal deaths per thousand deliveries declined from 3 89 to 0 09 from the first 5 year pe (1911–1915) to the last 5 years of the observation time 1–1975) The three main causes of maternal deaths peral fever haemorrhage and toxaemia are discus Since the new Maternity Clinic at Landspitalinn ed in 1949 it has been the main department for ob- ics and gynecology in Iceland to which a great major f complicated cases in pregnancy and delivery are red Since 1949 39411 women have delivered at this rtment There have been 15 maternal deaths at the or 0 4 per thousand A separate table (Table III) rs the age parity and causes of death in the 15 cases rnal deaths in Iceland during the last decade occur ne per 11 000 deliveries This is a problem of com ication as well as a medical problem

DEFINITION

his report on maternal deaths in Iceland are uded all women who died after the 28th week of gnancy those who died during delivery and ing the first 8 weeks after delivery irrespective he cause of death

INTRODUCTION

aw requiring a death certificate for all deaths was sed in Iceland in 1911 Consequently quite accu sources concerning the various causes of ths in Iceland are available since that year The Statistical Bureau of Iceland has collected all th certificates since 1911 and publishes data cerning the various causes of death at 5 to 10 r intervals (1)

In a recent report on deliveries in Iceland in the past (2) various aspects of maternity services was discussed and maternal deaths since 1881 summarized

As mentioned in the report there have been remarkable changes in the maternity services in Iceland particularly during the last three decades

Landspitalinn—the University Hospital—was established in 1930 It included a small maternity unit of 14 beds in fact the first maternity department in the country

Originally this unit was supposed to take care of complicated cases only Prior to this time practically all women in the country had delivered at home

During the following two decades a number of maternity homes and rural hospitals were founded The number of deliveries at these institutions increased steadily as the years passed

In 1949 a new department of obstetrics and gynecology opened at Landspitalinn with approximately 60 beds This department has since its opening accounted for approximately 40% of all deliveries in Iceland and the majority of all complicated deliveries

Presently 99% of all women in Iceland deliver in hospitals and maternity homes and over 70% in hospitals supervised by specialists in obstetrics and pediatrics

MATERNAL DEATHS SINCE 1911

Table I shows the main causes of maternal deaths in the country 1911–1975 the total number of deliveries and death rate per 1 000 deliveries at 5 year intervals

In spite of the small number of cases Table I shows clearly that the same evolution has taken place in Iceland as in other countries

Table I *Maternal deaths in Iceland 1911–1975*

	Causes of maternal death						
	Puerperal fever	Haemor rhage	Eclampsia toxaemia	Other causes	Total	Total number of deliveries	Maternal deaths per 1 000 deliveries
1911–1915	19	7	14	6	46	11 806	3 89
1916–1920	15	1	8	12	36	12 579	2 85
1921–1925	23	3	9	5	40	13 162	3 03
1926–1930	13	13	8	3	37	13 661	2 71
1931–1935	12	14	3	7	36	13 461	2 67
1936–1940	10	7	4	7	28	12 430	2 25
1941–1945	13	8	10	8	39	15 818	2 46
1946–1950	4	6	7	4	21	19 278	1 08
1951–1955	1	1	6	5	13	21 451	0 61
1956–1960	0	5	5	1	11	24 179	0 46
1961–1965	1	3	4	2	10	23 931	0 41
1966–1970	0	1	1	0	2	21 811	0 09
1971–1975	0	1	1	0	2	22 374	0 09
Total	111	70	80	60	321	275 891	1 4[illegible]

Puerperal fever was a rather common cause of maternal death until the end of the second world war when chemotherapeutics and antibiotics came into common use During the last 25 years there have only been two maternal deaths caused by puerperal fever registered

Haemorrhage before during or after delivery has been a rather common cause of maternal death Better facilities and therapy in the birth institutions (shock therapy blood transfusions etc) during the last three decades explain the lowering of maternal death in this group

The third main group of maternal death—eclampsia—toxaemia has declined remarkably during the last 25 years as well as the fourth group— other causes As mentioned earlier the main reason for the decline in maternal death by the above named causes is a better antenatal care in the country as well as better communication between the local health personnel and the major birth institutions

Under the heading other causes are listed various diagnoses such as pulmonary embolism apoplexy heart diseases cancer etc Finally Table I shows that the maternal deaths in Iceland have decreased from 3 89 per 1 000 at the beginning of the observation period to 0 09 per 1 000 deliveries at the present time

Table II *Number of deliveries and maternal deaths at the Landspitalinn Maternity Clinic 1949–1975*

Years	Number of deliveries	Maternal deaths	Maternal deaths per 1 000
1949–1960	19 247	11	0 6
1961–1975	20 164	4	0 2
Total	39 411	15	0 4

MATERNAL DEATHS AT THE LANDSPITALINN MATERNITY CLINIC

As mentioned earlier the new Maternity Clinic at Land[illegible] spitalinn opened in 1949 During the next decade [illegible] cated cases of pregnancy and delivery were [illegible] the new department from various parts of the co[illegible] an ever increasing scale During this period [illegible] tions by land and particularly by air made the tra[illegible]

Table III *Causes of maternal deaths at the Land[illegible] spitalinn Maternity Clinic 1949–1975*

No	Year	Age	Parity	*Causes of death*
1	1950	25	IV	Haemorrhagia post [illegible] placentae
2	1950	38	0	Haemorrhagia post [illegible] uteri
3	1952	29	III	Ruptura uteri
4	1953	35	0	Eclampsia
5	1954	25	I	Toxicosis matris. Haemo[illegible] rhagia et emolli[illegible]
6	1954	25	0	Embolia pulm post sect[illegible] Caesarea
7	1955	34	II	Eclampsia
8	1955	24	I	Incompensatio cordis [illegible] cordis congen
9	1956	33	II	Ruptura uteri
10	1956	47	I	Preeclampsia. Abl[illegible] placentae
11	1959	44	V	Apoplexia cerebri
12	1961	23	0	Cancer ovarii
13	1965	41	VII	Embolia pulmonis
14	1971	27	0	Eclampsia
15	1971	30	II	Haemorrhagia post [illegible] cervicis uteri

All diagnoses confirmed by autopsy

ts within the country easier even from the most te areas

21 maternal deaths during the years 1946–1950 only occurred at the Landspitalinn Maternity Clinic

t of 34 women who died during the 15 year period 1965 nine died at the Maternity Clinic but from the who died during the last 10 years two died at the and in fact both during the latter half of the period ring the last decade practically all high risk cases been admitted to institutions offering the best ties

ble II shows the number of deliveries and maternal is at the Landspitalinn Maternity Clinic since 1949 first 11 years are compared with the last 15 years ie number of women in each group is comparable

ble III shows the causes of maternal deaths at the ispitalinn Maternity Clinic since 1949

rther analysis of the causes of death shows that six nts died from haemorrhage caused by rupture of the is in three cases Four cases were moribund on arri

ur died from eclampsia three shortly after arrival to department Two died suddenly from pulmonary olism several days after delivery Both of them had an nsive thrombo-phlebitis in the femoral and iliac veins

is leaves three patients who died from causes not ed to pregnancy or its complications

Congenital heart disease

Cerebral apoplexy where postmortem examination aled aneurysm of the cerebral arteries

Cancer of the ovary discovered by an explorative otomy when the patient was 4 months pregnant She widespread metastases and ascitis already at that An attempt was made to save the child by Caesarean ion in the eighth month of pregnancy but the baby from hyaline membrane disease on the second day mother succumbed to her disease ? weeks after the ration

DISCUSSION

is material shows that maternal deaths in Ice d are a rare problem at the present time During the last 10 years four women out of the 44 000 who delivered died or one per 11 000 deliveries

Iceland is a sparsely populated country of 103 000 square kilometers (over 40 000 square miles) with a population (1976) of 220 000

Seventy to eighty per cent of the population lives within reasonable distance from hospitals and de livery homes However for several years to come approximately one fourth of the population will continue to live far away from hospitals and in a few instances in very remote areas

Thus we are well aware of the fact that some parts of the country are denied modern hospital facilities during the winter season and accidents will happen away from hospitals birth catastrophes as well as other acute diseases or traumata

In conclusion maternal deaths in Iceland are to-day a problem of communications as well as a med ical problem

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MATERNAL MORTALITY IN AUSTRALIA 1964–72

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ract Statistics covering deaths directly due to preg cy in the Commonwealth of Australia have been avail since the turn of the century However those for hs associated with pregnancy have not Over the past decades each State in the Commonwealth has set up ernal Mortality Committees to collect confidential in ation on each maternal death both direct (where the h is directly attributable to pregnancy or childbirth) associated (where the death is associated with but not ctly due to pregnan y or childbirth) New South Wales set up the first such Committee in the 1930 s and this since been followed by the other States Most of the es have published reports from time to time but ow to the small numbers involved these reports have n limited in the conclusions that could be made Con ntial information on each maternal death is obtained is considered by the State *Maternal Mortality Com* tee The cause of death is confirmed and classified A ropsy is usually performed in each instance the path gist travelling to the town where the death has occur if requested

en all the information is collected the case tory is assessed and a decision made as to ether there has been a primary avoidable factor sent Such a factor is judged to be present if re has been some departure from accepted ndards of satisfactory care which may have yed a part in the ensuing death It is not sug sted that in all cases in which avoidable factors considered present death could certainly have en prevented but the presence of an avoidable tor is regarded as an indication that the risk of ath could have been at least materially lessened it is decided that there is an avoidable factor esent further classification is made as to whether e medical attendant the hospital or the patient s been responsible for the departure from ac pted practice Due cognizance is taken of the ographical area where the death has occurred the ilities that have been available and the status of e medical attendant

The individual State and Territory statistics have been collected and published compositely on a triennial basis the first one being for 1964-66 fol lowed by reports for the years 1967–69 and 1970–72

The purpose of the reports is one of education to inform the medical and nursing profession of the major causes of death and to highlight the avoidable factors found and so improve the obstetric service of the country

There were 275 maternal deaths in the first trien nium (1964–66) 237 in the second (1967–69) and 244 in the third (1970–72)—a total of 756

Table I gives the approximated maternal mortal ity rates for each triennium It is noted that there has been a significant reduction in the deaths di rectly due to pregnancy in the last triennium whereas there has been no change in the number of associated deaths in the three triennia An attempt to explain the reason for this reduction will be made later in this paper A comparison between the deaths in Australia directly attributed to pregnan cy—18 96 per 10 000 live births in 1970–72—to other countries reveals that Scandinavian countries vary between 10 8 and 18 0 England and Scotland approximately 20 and Canada and USA 26

Table II shows the incidences of the five main causes of death over the three 3 year periods Although the condition was present it may not have been the *major* cause of death These condi tions will be discussed individually

Haemorrhage

This the largest group is made up of several differ ent conditions namely abruptio placentae (22) placenta preaevia (13) ruptured uterus (35) ectopic pregnancy (19) and post partum haemorrhage (52) Assessment of the histories showed that there was an avoidable factor in over 66 % of cases

Table I *Approximate maternal mortality rates*

Triennium	Total no of con finements	Maternal deaths Number	Rate per 10^5 confinements
1964–66	667 649	202 (73)[b]	30 25 (10 93)
1967–69	713 064	166 (71)	23 27 (9 95)
1970–72	790 818	150 (94)	18 96 (11 88)
1964–72	2 171 531	518 (238)	23 85 (10 96)

Deaths directly attributable to pregnancy or childbirth
[b] Deaths associated with pregnancy or childbirth but not directly due to pregnancy or childbirth

The importance of treating anaemia during preg nancy the availability of blood and its prompt and adequate replacement cannot be stressed enough Prevention of blood loss by prophylactic oxytocics and the careful repair of lacerations can avoid many haemorrhages Routine grouping and estimation of haemoglobin levels in all patients is a necessity It must not be forgotten that the number of deaths in which an avoidable factor was considered present is only the tip of the iceberg There are many patients who almost die from haemorrhage be it ante intra or post partum The prevention of these near misses is also essential

Some of these deaths occur in remote parts of the country where the aborigine who refuses medical aid during pregnancy and childbirth lives Another problem is the storage of blood in remote areas In rare instances a massive transfusion is required to save the life of the mother and the amount of blood vailable may be insufficient The continued oc rrence of death from ectopic pregnancy is due to either misdiagnosis on the part of the practitioner or to failure of the patient to call the doctor Deaths due to ante partum haemorrhage are not great but in each instance an avoidable factor is usually present

Infection

Deaths from infection have remained remarkably constant over the nine year period The infection is usually classified as genital or extra genital in origin Included under the classification of genital sites are deaths due to septic abortion and those associated with vaginal delivery and Caesarean sec tion

The 41 deaths associated with septic abortion will be mentioned later There were 15 deaths as sociated with Caesarean section Bacteraemic shock was not a common cause of death [illegible] In the extra genital sites pulmonary inf[illegible] was the commonest cause of death Any [illegible] fection in pregnancy must be regarded se[illegible] especially if there is a cardiac complication [illegible] present or if an anaesthetic is required [illegible] with pre existing bronchiectasis or asthma [illegible] under constant supervision during the [illegible] months when viral infections are more com[illegible]

Most deaths from infection must be regarded [illegible] avoidable If any impact is to be made on [illegible] as a cause of death a 24 hour adequate bacterio[illegible] ical service must be available so that the [illegible] antibiotic can be given Prophylactic an[illegible] cover is necessary in specific obstetric sit[illegible] *and bacteraemic shock must be thought* [illegible] whenever a patient collapses immediately after [illegible] livery

Pulmonary embolism

Deaths from pulmonary embolism are usually [illegible] expected and very distressing for the rel[illegible] Table II shows the number of deaths in each tri[illegible] nium and the times of their occurrences There [illegible] a marked reduction in the number of deaths in the last triennium

Deaths after vaginal delivery were the [illegible] factor in this reduction In the first triennium de[illegible] without warning far outnumbered those in [illegible] there was a warning in the last tri ennium the numbers were about the same Only half of the patients with warning signs had treatment De[illegible] during pregnancy usually occurred in the [illegible] multigravid patient with varicose veins [illegible] examined was found to have a deep [illegible] thrombosis Deaths after Caesarean secti[illegible] rare especially since early ambulation and a l[illegible] dose heparin regime have now become routine

An interesting observation regarding the [illegible]

Table II *Incidences of main causes of m[illegible] mortality*

Cause of death	Years 1964–66	1967–69	1970–7[illegible]	T[illegible]
Haemorrhage	75	47	41	[illegible]
Infection	47	38	41	[illegible]
Pulmonary embolism	38	43	22	[illegible]
Abortion	45	5	3[illegible]	[illegible]
Toxaemia	43	[illegible]	1	

III Pulmonary thrombo-embolism

	Number of deaths		
	1964–66	1967–69	1970–72
during pregnancy	3	15	5
after vaginal ery	22	23	10
after Caesarean on	13	5	4
after abortion	6	–	2
after operation for pic pregnancy	–	–	1
	44	43	22

m deaths is the time at which the embolism rs Approximately 25% occur within 24 hours livery and another 25% within the first week reakdown of patients dying from pulmonary olism reveals that the risk increases with age parity This may be the reason for the fall in the ber of deaths for over the nine years studied number of elderly multigravidae has been mar y reduced As nations come more to zero popu n growth deaths from pulmonary embolism become much less Meantime the patient with greatest risk is the obese elderly multigravidae severe varicosities of the lower extremities ning signs are more common in the patient who an ante partum embolus The use of anticoagul has now become routine when deep vein mbosis is diagnosed and after Caesarean sec when low dose heparin is used

rtion

ths following abortion continue to occur despite relaxation of indications for legal abortion in the ntry The partial elimination of untrained tionists has not markedly reduced the number deaths which has always been low in any case ths following legal abortions are now occur indicating that the procedure is not without The two main causes of death following abor are sepsis and haemorrhage sepsis being the re common However it must be noted that in h triennium less than 15 women died in Australia m septic abortion

n scrutinizing deaths from abortion it is noted a proportion die from the condition for which abortion was performed In others the techni of the medical attendant was faulty In the vast majority the pregnancy could have been prevented if the patient had availed herself of contraceptive advice which is available or had she immediately changed from one technique which was not suiting her to another In theory because therapeutic abor tions are carried out to save life all deaths in this group should be avoidable

Toxaemia

Included in this group are patients who died from pre eclampsia eclampsia and acute yellow atrophy of the liver It is regrettable that the country which led the world in the concept that eclampsia was preventable and severe pre-eclampsia could be avoided still has deaths from these two conditions With adequate ante natal care pre-eclampsia can usually be detected early and if treated adequately should not be responsible for maternal deaths Early induction of premature labour is the only sure way of controlling the condition regardless of the period of gestation Most of the deaths in this group are classified as preventable the medical manage ment is the major cause and factors relating to the patient make a significant contribution The actual cause of death is usually a cerebral haemorrhage coagulation problems and liver failure are the next two causes in order of frequency

In this group the majority of deaths occur in the teenager in her first pregnancy This is in con tradistinction to some of the other causes of death already discussed As well as this young age group deaths are found in those women who commence the pregnancy with essential hypertension or chronic renal disease When pre ecampsia is superadded the mother s life can be at risk There are less deaths in this group than previously as these pregnancies are being terminated more fre quently these days

Although not connected with the above group deaths from subarachnoid haemorrhage and cere brovascular accidents are included In this group the death is usually unavoidable and unexpected When added to deaths from cerebral haemorrhage in patients with pre eclampsia or eclampsia it forms one of the commonest causes of maternal death

There are other important causes of maternal deaths that are not included in this short paper These are cardiac disease associated with preg nancy Caesarean section complications of an aesthesia ruptured uterus amniotic fluid and air

embolism suicide traffic accidents and associated neoplasia

Each country will have special problems which may justify a maternal death rate a little higher than her neighbour In Australia such problems are our distances and our aboriginal population In any comparison with other countries the abortion rate must also be quoted for in many developed countries most patients at risk have pregnancies terminated or the country has achieved zero population growth and so eliminated the major group at risk the elderly multigravidae

Taking all this into consideration there is no doubt that we can reduce the incidence of deaths directly due to pregnancy even more than we have done in the last triennium

Deaths associated with pregnancy comprise the smaller of the two groups and the number has remained stationary over the nine year period Most of these deaths are unavoidable and therefore a reduction will be more difficult

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INHIBITION OF PUERPERAL LACTATION

A Double Blind Study of Bromocriptine and Placebo

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tract Bromocriptine and placebo were randomly ated for three weeks to 5? postpartum patients re ing lactation suppression Bromocriptine significantly red plasma prolactin levels and suppressed breast breast pain and engorgement quicker than placebo side-effects were noted and rebound lactation did not or Menstruation appeared to re start sooner when mocriptine was given

man breast milk is the most complete and satis ng supply of nutrition the neonate can receive re are however times when breast feeding is ppropriate and a safe effective means of lacta n suppression is indicated

Hitherto simple measures such as a good support the breasts analgesics and diuretics have been d or oestrogen/androgen combinations or trogens alone administered The latter acting ectly on breast tissues (1) are effective but in ase the risk of thromboembolism

Lactogenesis is dependent on the raised level of itary prolactin secretion Recent papers (1–10) ve suggested that this can be lowered by the pamine agonist Bromocriptine thus effectively ppressing lactation

However the optimum dosage to minimise side fects such as rebound lactation and the possi lity of stimulating early ovulation has not yet been lly explored hence at Queen Charlotte s Hospi l London a double blind randomised study of the fects of Bromocriptine in comparison with place was carried out Specific reference was made to aluation of plasma prolactin levels lactation in bition during and after treatment breast pain and gorgement and the onset of menses This paper resents the results

MATERIAL AND METHODS

(a) Patients

Informed consent to take part in the study was sought from parturient patients in Queen Charlotte s Hospital London who did not desire to breast feed Fifty two pa tients embarked on the trial but only 36 returned suffi cient data for analysis

(b) Drugs

All patients were randomly allocated indistinguishable capsules of "active Bromocriptine (2 5 mg) or a pharma cologically inactive placebo to be taken two daily for four teen days from day 0 (delivery) and one daily for a further seven days

(c) Data collection

1 *Patients symptoms* After instruction the patients were asked to fill in and return after 28 days data cards (Fig 1) concerned with milk production breast engorge ment and breast pain

2 *Blood sampling* 10 ml peripheral venous blood were taken within one hour of delivery (day 0) 48 hours after delivery (day ?) and 7 days post-delivery After centri fugation plasma was stored at −?0°C until assay

(d) Assay

Assay was performed by the double antibody radioim munoassay method modified from a method previously used for human placental lactogen (11) After iodination with chloramine T (35 μg for 30 sec) prolactin was puri fied on a sephadix G100 column (1 5×70 cm) The elution buffer contained 0 1% bovine serum albumen (BSA) The assay buffer contained 2 5% BSA Incubation continued for three days with the first antibody one day after addi tion of labelled prolactin and one day after antirabbit gamma globulin serum Dilute horse serum (0 1 ml 25% in assay buffer) was added to all assay tubes With this method no cross reaction between the prolactin anti serum and HCG (1000 i u) LH/FSH (500 i u) HPL (32 ng) and growth hormone (63 ng) was found (1)

D tes														
D ys f tr tm t / P ro ete	1	2	3	4	5	6	7	8	9	10	11	12	13	
Milk P ducti (Try P lpation)														
Co g ti														
Po														

S e f 4 p ints 0 no milk 1 m drops 2 slight outflow 3 streo f ilk

S of 4 point 0 ab t 1 mild 2 m derote 3 se ere

Comm nts/Sid Eff cts:

Fig 1 Part of patients data card and score sheet

RESULTS

1 *Prolactin levels (Fig 2)*

At day 0 there was no significant difference in plasma prolactin levels of the two groups whereas by day 2 the level was significantly lower in patients taking Bromocriptine ($p<0\ 001$) By day 7 this difference had lessened with descent of the placebo group prolactin level but it was still significant ($p<0\ 02$) At six weeks levels were down to normal (shaded) area but the number of samples col ted then was insufficient to warrant inclusion

2 *Milk suppression (Table I)*

Throughout the 28 days post delivery the active Bromocriptine regime was considered by the patients to be significantly better in suppressing lactation ($p<0\ 01$) As 100% suppression at four weeks was reported in the Bromocriptine group no rebound lactation therefore occurred in the week following termination of therapy

3 *Breast congestion (Table II) and breast pain (Table III)*

The greatest significant improvement on Bromocriptine of these symptoms when compared to placebo was noted in the first seven days ($p<0\ 01$) which is when the most discomfort is reported

4 *Menstrual pattern (Table IV)*

There was a definite trend towards earlier re of menses in the active Bromocriptine gr although menses were still absent in similar n bers in both groups This difference may be i fluenced by the greater number of patients in placebo group who failed to return for post check up thus forcing their subsequent menstru history to be classified as unknown

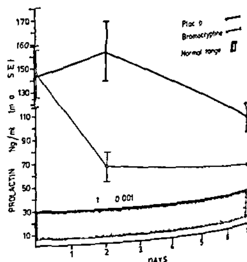


Fig 2 Comparison of prolactin levels for one week p parturition

le I *Milk suppression*

ys		14 Days		21 Days		28 Days	
ve	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
))	1/17 (6%)	14/20 (70%)	3/16 (19%)	16/18 (89%)	5/15 (33%	17/17 (100%)	10/17 (59%)
$p<0.01$		$p<0.01$		$p<0.01$		$p<0.01$	

DISCUSSION

partum lactogenesis is closely related to the etion of prolactin by the pituitary (13) During mancy prolactin secretions have reached a level but the lactogenic action is opposed by hi h circulating levels of oestrogen and pro-erone of late pregnancy Dopamine normally bits prolactin secretion at pituitary level (14) but regnancy is overcome by the increased prolactin ut from the enlarged prolactin secreting pitui cells Hence when the inhibitory effect of r hormones is removed around parturition ogenesis occurs

romocriptine as a Dopamine agonist inhibits la tin secretion (15) by its stimulatory effect on amine receptors in the hypothalamus thus en cing prolactin inhibitory hormone secretion and perhaps by a local action at pituitary level Therefore if given at the right time in suffi nt quantity Bromocriptine inhibits prolactin retion and stops lactation

he thesis is supported by the results of this er for within two days there was a significant ering of serum prolactin levels in patients using mocriptine when compared to placebo ($p<$ 01) This significant difference is continued at 7 s ($p<0.02$) and accounts for milk production in ition in 60% of Bromocriptine patients com ed with 6% on placebo and consequent signifi nt differences in pain and congestion ($p<0.01$)

Bromocriptine is also reported to be of use in suppressing galactopoiesis (5) which also depends on prolactin Although it is known that prolactin levels can be back to normal within three weeks of parturition (18) a wide fluctuation is noted which may be related to the stimulatory action of the suck ing reflex (6) These factors could account for re ports of rebound lactation (4 7) when shorter dos age regimes were used To overcome this in our study 5 mg daily was given for two weeks followed by 2 5 mg for a further seven days Results show that 100% of treated patients reported dry breasts one week after cessation of Bromocriptine therapy

Pain and congestion were not significantly dif ferent after the first week but it is of course during this time that pain is most troublesome

Removal of the gonadal inhibitory effect of hyperprolactinemia *causes ovulation in the galact* orrhoea amenorrhoea syndrome (19 20 21) This can also occur in the parturient patient and makes early conception a distinct possibility (22) Six weeks after delivery menses had returned in 40% of the Bromocriptine group compared with 22 7% on placebo The high drop-out rate however makes these figures unreliable although note should be taken of the trend

At the dosage used therefore Bromocriptine is a safe effective suppressor of lactation Such pro-longed therapy does not however lend itself to consumer preference and further studies are needed

ble II *Breast pain relief*

ays		14 Days		21 Days		28 Days	
tive	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
[illegible]20 [illegible]%)	4/17 ([illegible]4%)	17/20 (85%)	13/16 (81%)	18/18 (100%)	13/15 (87%)	17/17 (100%)	15/15 (100%)
$p<0.01$		NS		NS		NS	

Table III *Breast congestion relief*

7 Days		14 Days		21 Days		28 Days	
Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
14/20 (70%)	2/17 (12%)	17/20 (85%)	13/16 (81%)	18/18 (100%)	13/15 (87%)	16/17 (94%)	14/15 (93%)
$p<0.01$		NS		NS		NS	

Table IV *Menstrual pattern*

Menses	Bromocriptine	Placebo
% returned	40	22 7
% absent	33 3	31 8
% unknown	26 6	45 45

to formulate the ideal regime Additional work is also necessary to see whether indeed ovulation and menses are brought forward and whether users of these drugs should have contraceptive measures recommended earlier than is usual

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PROLACTIN RESPONSIVENESS TO TRH IN AMENORRHEIC WOMEN WITH AND WITHOUT GALACTORRHEA

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[Abstr]act. Sixty women were given intravenous injection [of 2]00 µg TRH to assess its diagnostic potential as a [stim]ulus to PRL release. Following the administration of [TR]H there was a prompt increase in serum PRL to [illegible] in normal women, [illegible] patients, non tumoral galactorrheic cases, [and] patients with pituitary tumors respectively. The TRH [respo]nse above baseline of PRL levels was statistically [signi]ficant in all groups but the women with pituitary [tum]ors which showed a blunted response. The per cent of [incr]ement of PRL levels after TRH was similar in amen[orrh]eic women regardless the presence or not of galac[torr]hea; this increase was significantly greater than in pa[tien]ts with pituitary tumors ($p<0.01$). The per cent of [incr]ement above baseline of PRL was significantly greater [in m]enstruating women than in amenorrheic patients [($p<$]0.001). In basis of present data: 1) there is a dim[inis]hed PRL secretion after TRH in amenorrheic women [rega]rdless the presence of galactorrhea or hyperprolactin[emi]a; 2) a blunted response to TRH in hyperprolactinemic [wom]en may be indicative of a pituitary tumor.

[Stu]dies to asses the validity of prolactin (PRL) se[cre]tion in response to synthetic thyrotropin releas[ing] hormone (TRH) to differentiate galactorrhea [wom]en with or without pituitary tumors have yield[ed] controversial reports (1–2). We have proposed [in a st]udy that a blunted response to TRH injection [in hy]perprolactinemic women may be indicative of [a t]umoral origin (7). Present investigation was di[rec]ted to evaluate the TRH-induced PRL secretion [in] a larger series of galactorrheic women and for [com]parison patients with amenorrhea of presumed [hy]pothalamic origin as well as normal menstruating [w]omen were included in the study.

MATERIAL AND METHODS

[A tot]al of 61 amenorrheic women either with or without [gala]ctorrhea were tested in their PRL secretory reserve by the intravenous use of 200 µg TRH according to our procedure (7). In the group of patients with amenorrhea and galactorrhea, 11 out of the 42 had an enlargement of the sella which was considered compatible with pituitary adenoma. The remaining 19 out of the total series of 61 patients had only amenorrhea presumably of hypothalamic origin. In this group the following diagnosis were established: [illegible] cases of [illegible], [illegible] cases of anorexia nervosa, [illegible] cases of psychogenic amenorrhea, and 9 cases of abnormality in the estrogen feedback mechanism. Six normal menstruating women were included in this study in order to evaluate their PRL responsiveness to TRH. All women had both clinically and by the laboratory tests a normal thyroidal function. Serum PRL was measured by radioimmunoassay according the method of Hwang (4); sensitivity and interassay variation in our laboratory has been reported previously (5). Unpaired and paired Student's t-tests were used to compare the results.

RESULTS

Normal women

In the six normal women the basal values of PRL ranged from 2 to 13 ng/ml with a mean value (±S.E.M.) of 9.2±2.8 (Fig. 1). In response to 200 µg TRH, hPRL levels had a maximum increase of 98.6±L[illegible] ng/ml (mean ±S.E.M.) which was statistically significant ($p<0.001$). The maximum increase in these six patients showed a range from 56 to 160 ng/ml.

Amenorrheic women without galactorrhea

In this group four out of the 19 patients were hyperprolactinemic despite the absence of galactorrhea. Baseline PRL ranged from 4 to 6[illegible] ng/ml with a mean value (±S.E.M.) of 22.1±3.3 (Fig. 1). TRH injection elicited a mean maximum increase in hPRL levels of 6[illegible].8±10.9 (±S.E.M.); this rise was

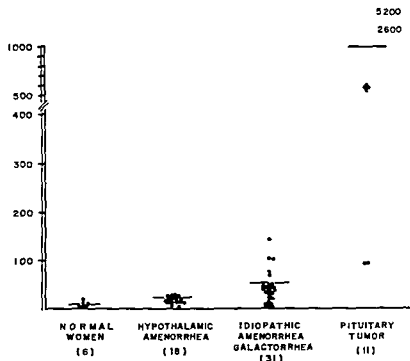


Fig 1 Basal serum PRL are pre[illegible]sented on the vertical axis in [illegible] women and amenorrheic pa[illegible] Mean PRL values represented [illegible] horizontal bar was higher in ga[illegible]torrheic women Patients with pituitary tumors had the highest PRL concentrations

statistically significant ($p<0\ 001$) The maximum increase ranged from 26 to 170 ng/ml

Idiopathic amenorrhea galactorrhea

The mean of baseline PRL levels was 54 7±12 2 ng/ml (±S E M) and the maximum increase after TRH was 98 4±13 1 ng/ml (mean ±S E) which [illegible]as significant ($p<0\ 01$) PRL increments ranged [illegible] 12 to 360 ng/ml PRL secretion in response to [illegible]H was similar in both groups of amenorrheic [illegible]omen regardless the presence or not of galactorrhea conversely the amenorrheic women had a lesser PRL secretion after TRH than normal women ($p<0\ 001$) as shown in Fig 2

Galactorrheic women with pituitary tumor

Women in this group presented the highest basal PRL levels with a range from 90 to 5200 ng/ml the mean value (±S E M) was 1086 5±482 2 ng/ml Mean maximum increase after TRH was 1382±602 7 (±S E M) This response was not statistically significant The mean maximum increase of PRL above baseline in women with a tumoral process was significantly less ($p<0\ 001$) than in both groups of hypothalamic amenorrhea and idiopathic galactorrhea (Fig 2)

DISCUSSION

In this study of amenorrheic patients is conf[illegible] that elevated levels of PRL may occur in the [illegible]sence of galactorrhea and conversely patients [illegible] galactorrhea may be found to have normal [illegible] levels (2 6) It was also evident that patients with pituitary tumors presented the highest PRL levels which leads to consider that those cases e[illegible] PRL values above 100 ng/ml require prolonged follow up despite the normality of pituitary [illegible] tomography The release of PRL in response to TRH in amenorrheic women with or without gala[illegible]torrhea showing no evidence of pituitary tumor [illegible] significantly less than in normal wome[illegible] S[illegible] responses to TRH in patients with hypothalamic [illegible] pituitary disturbances have been reported [illegible] on the other hand exaggerated responses to TR[illegible] have been reported in patients with hyperprolactinemia (8) However the studies with the larger se[illegible] of patients indicate that women having a [illegible] of patients indicate that women having a [illegible] thalamic disturbance expressed cl[illegible]cally by [illegible] amenorrhea or galactorrhea show less release of PRL after TRH stimulation than normal women It has been suggested that an "ultra-short feed back effect of the PRL on the normal [illegible] lactotrophes preventing a normal release of P[illegible] TRH could be operative (?) but the demonstra[illegible] by us that a diminished response to TRH [illegible]

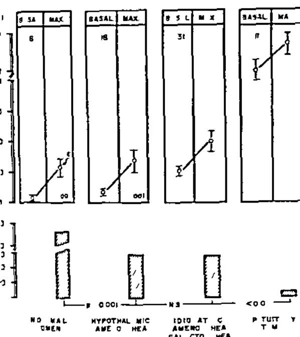


Fig 2 Release of PRL in response to TRH Responses are expressed as maximum increase above baseline and as per cent increment from the basal values

ed in amenorrheic women regardless the presence or not of elevated PRL levels weighs against this hypothesis

It seems that patients with amenorrhea galactorrhea syndrome present a varied response to the stimulating and inhibiting tests of hypothalamic pituitary function (3) We can conclude from the present study that although basal serum PRL levels do not distinguish women with tumoral process from those with hyperprolactinemia of other etiologies administration of TRH may be helpful in separating patients with pituitary tumors from those with galactorrhea of other causes This is in agreement with our previous studies (3 9) in which was suggested that elevated PRL levels associated with blunted response to TRH and absent or deficient secretion of both gonadotropins in response to LH-RH could be indicative of an underlying pituitary microadenoma

ACKNOWLEDGEMENTS

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TRIAL OF A NEW ANALOGUE OF LH RH IN NORMAL SUBJECTS AND IN CASES OF *ANOVULATORY STERILITY*

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act A new and potent analogue of luteinizing one releasing hormone (LH RH) the des gly 6-D LH RH which was synthesized in 1975 by Schally his group was assessed in normal volunteers both and women and in six cases of anovulatory sterility new substance seems to be one *of the most active* and LH releasing factors Its effect is stronger in the le than in the male acting more actively on LH than release The magnitude of the effect is greater not in amount but also in time the levels of gonado- ins after the injection being higher and remaining longer This last property makes the new substance ally suitable for the treatment of anovulatory steril Of six sterile women one ovulated and two became nant

releasing effect on LH and to a lesser extent SH secretion by a decapeptide obtained from hypothalamus of the pig is today very well wn through numerous research works in the seven years Two years ago Schally s group) began to investigate the possible action of e analogues of the synthetic decapeptide The pounds assayed were *D* ala-6 des gly NH_2 10-RH-ethylamide (2 5 6 8 10) *D lys 6-LH RH* des gly 10 pro-9-ethylamide LH RH (3 7) gly 10 pro-9 propylamide LH RH 3 and *D* leu es gly NH_2-10-pro-ethylamide LH RH (9) The e research group (4) has investigated the possi y of introducing a *D* tryptophan group in posi 6 in the decapeptide The so obtained *D* pt LH RH was sent to our group for clinical ing at the end of 1975

MATERIAL AND METHODS

study is divided into two parts In the first one the ct of the analogue was compared with that of synthetic LH RH Nine normal healthy and menstruating women volunteers—chosen among students and nurses aged from 18 to 6 years were followed during two previous cycles monitored by temperature charts vaginal cytology and pregnanediol determinations in order to prove their nor mality During the late follicular phase (12–14 days) of the third cycle each volunteer was injected with 100 μg of LH RH intravenously and tested for LH and FSH in plasma by double radioimmunoassay against the NIH kit The samples of blood were taken at zero time and after 15 30 45 60 90 and 120 min

The same control or pattern curves were obtained from eight normal student boy volunteers ranging from 18–22 years old

Six girls also volunteers and normal were tested with only 10 μg of *D*-6-trypt LH RH but in such cases the *extraction times were prolonged up to 180 240 360 and* 480 min because the first assays showed that its action was delayed

Another group of young normal women was tested with graduated dosages of the analogue 1 5 7 5 and 10 μg Finally six normal boys were tested in the same way as the girls They were also normal students volunteers aged from 19 to 23 years

The second part of the study concerned sterile an ovulatory women The group was composed of six wom en aged from 31 to 36 years whose sole cause of infertil ity was anovulation Basic requirements for this diagnosis were 1) flat temperature charts for a minimum of four months 2) endometrial biopsies showing monophasic cycle in two consecutive cycles 3) low pregnanediol excretions in the second half of at least three consecutive cycles and 4) absence of other causes of sterility in the couple All the six women were monitored in a previous cycle with plasma FSH and LH every four days basal temperature and urinary pregnanediol estimations In a second cycle they were treated with an intravenous infu sion of 40 μg of *D*-6-trypt LH RH during eight hours fol lowed by a further 40 μg intramuscularly The time of the initiation of the treatment being the 13th day of the cycle FSH and LH estimations were done before the treatment and 15 30 45 60 90 1 0 180 240 360 and 480 min after the starting of the infusion

Fig 1 Effect of *D* 6-trypt LH RH (10 µg) compared with the action of LH RH (100 µg) on LH and FSH levels in plasma of normal young women (preovulatory phase)

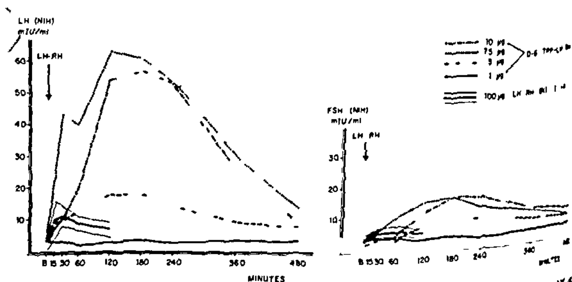
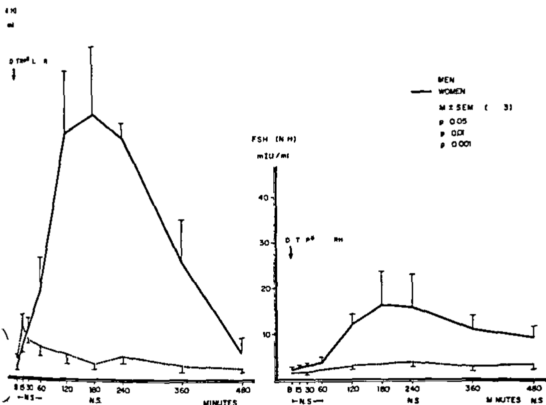


Fig 2 Effect of different dosages of *D*-6-trypt LH RH on plasma FSH and LH of normal women The shaded area shows the oscillations of FSH and LH el[illegible] of LH RH



3 Comparison of action of *D*-6-trypt LH RH on ma LH and FSH levels of men and women

RESULTS

results are shown graphically in Figs 1–4 In 1 is seen the effect of 10 μg of *D* 6-trypt RH intravenously on the plasma levels of H and LH The results in six normal young men were compared with another 9 normal ing women injected with a tenfold dose of conventional LH RH The response of plasma LH is % higher with the analogue than with the conventional LH RH Using also the *D*-6-trypt LH RH the gth of the response is eightfold (800%) compared h LH RH

The FSH response although not so great is also y significantly increased approximately 300% her and 400% longer The importance of these ferences is very remarkable because there is a neral agreement that the pulse of FSH and LH is elicited by current LH RH too short to induce ulatory changes at the ovarian level It should be mphasized that the higher and longer responses were obtained with only one tenth the dosage of the analogue as compared with the conventional LH RH

Fig 2 shows the effects of an increasing dosage in individual cases One microgram has practically no effect but a dosage as small as 5 μg is able to promote as high but much more prolonged action as 100 μg of LH RH With 7 5 and 10 μg the effects are as described in Fig 1

In Fig 3 the differences between normal men and women are shown Six normal young men were compared with six normal young women In the male the responses are lower both in FSH and in LH This fact has not been described with conventional LH RH or other analogue compounds We should call attention to this difference

Finally six sterile anovulatory women selected as already described were treated with a total amount of 80 μg of *D*-6-trypt LH RH The outline of the clinical experiment was described above It should be emphasized that in all cases the

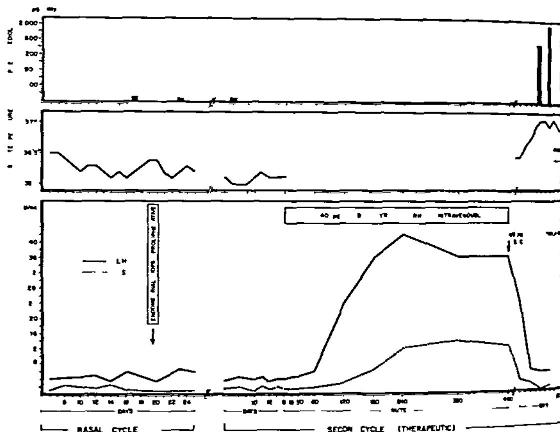


Fig 4 Pregnanediol basal temperature FSH and LH during two cycles in a sterile anovulatory woman In the second cycle there was injected a total amount of 80 μg *D*-6-trypt LH RH partly intravenous and partly intramuscular The woman became pregnant in the treatment cycle

tryptophan analogue was employed alone without any previous treatment with HMG HGC or Clomiphene Of the six women two became pregnant and in one more ovulation definitely occurred the two pregnancies one resulted in delivery of a healthy child and the other in an abortion In Fig 4 the results from the first pregnancy are shown

COMMENTS

The discovery and synthesis of porcine LH RH was followed by a great deal of hope in the successful treatment of anovulatory sterility and (or) amenorrhea However the results in clinical practice have not confirmed this preliminary expectation This was in part due to the short discharge of LH that is commonly obtained with the current dosages of the decapeptide The peak of the LH response to 100–200 μg takes place for no longer than 30–60 min It seems that such a short stimulation is not enough to provoke ovulation and the correct luteinization that must follow the expulsion of the egg The great advantage of the analogue that we are now using is not only its stronger action but the much longer effect Up to now we have only a very limited experience but we believe that this substance if associated with follicle stimulation with either HMG Clomiphene or both may be a very important tool in the treatment of ovulatory disturbances in woman

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DANAZOL AN ANTIGONADOTROPHIC AGENT IN THE TREATMENT OF RECURRENT PELVIC AND INTESTINAL ENDOMETRIOSIS

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ract Six cases of pelvic endometriosis were treated Danazol 400 mg daily for six months In four of these intestinal endometriosis of varying severity was present The initial results were very satisfactory pt in one case with adenomyosis and continuous spot Follow up after cessation of treatment suggests that me cases a further period of treatment will be neces

lazol a ? 3 isoxazol derivate of 17 α ethinyl osterone was recently made available to us for ical studies This steroid inhibits gonadotrophin retion/release but has no oestrogenic or proges onal action and only weak androgenicity at high e levels Since oestrogens may not be markedly pressed the degree of endometrial atrophy sug ts competition with oestrogens at the target tis in addition

he effect of Danazol has been studied in a vari of gynaecological and endocrine disorders such endometriosis precocious puberty chronic tic mastitis breast hypertrophy galactorrhoea nopausal symptoms and infertility Preliminary a indicate that Danazol may be of considerable lue in the management of pelvic endometriosis

A limited supply (from Sterling Winthrop Surbi) Surrey U K) has restricted our use of nazol to cases recurring after surgery and cases th pelvic as well as intestinal endometriosis Our tention was to study the effect of Danazol in such ses paying particular attention to clinical prog ss side effects and prognosis

METHODS

llowing a study of the literature we decided to adminis r Danazol orally at a dose of ?00 mg twice daily for six onths The patients were seen monthly for clinical as sessment The results from detailed metabolic and en docrine studies have been reported previously (1 4 6 7 9 11) and no further attention was paid to these aspects

PATIENTS

The series includes six cases with pelvic endometriosis of which four had varying degrees of additional involvement of the intestinal tract

Case I

A 3? year-old woman had suffered from irregular periods intermenstrual spotting dysmenorrhoea dyspareunia and primary infertility and she had undergone a laparotomy in 1974 The uterus contained a swelling possibly an in tramural fibroid while the peritoneum was sprinkled with endometriotic implants and the pouch of Douglas was closed by endometriotic tissue Involvement of both ovaries (diameter 4–5 cm) and also the serosa of the rec tum was apparent The swelling was excised from the anterior uterine wall and both ovaries resected Both specimens showed typical endometriosis

Treatment with a variety of hormonal preparations was followed by an unsatisfactory response

In July 1975 treatment by Danazol was started because of dysmenorrhoea dyspareunia lower abdominal pain during the latter half of the period and irregular periods with inter menstrual spotting The right ovary was 5–6 cm in diameter and the uterus and the left ovary almost nor mal

Six weeks later the symptoms had almost disappeared apart from spotting The uterus was now retroverted both ovaries normal and not tender Following treatment for three months a curettage was performed and subsequently a hysterectomy because of the continuous spotting throughout three years The ovaries were small and ad herent the pouch of Douglas closed by fibrous tissue A number of serosal adhesions were found but no visible endometriotic implants were present in the serosa

Follow up (14 months) The ovarian endometriosis re curred after 1? months Treatment with Danazol was re sumed with a satisfactory response

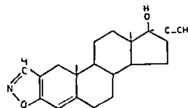


Fig 1 Chemical structure of Danazol

Case 2

A 28 year-old woman who had a curettage in 1971 for irregular periods Her uterus at that time was comparable to that seen in an 8 weeks pregnancy In 1972 both ovaries were resected being about 8–10 cm in diameter Diagnosis endometriosis

In subsequent years variable symptoms of lower abdominal pains during the luteal phase dysmenorrhoea dyspareunia menorrhagia and primary sterility were reported Various types of hormonal treatment failed

When Danazol was started in October 1975 the main symptoms were menorrhagia (periods about ten days duration) and pronounced dysmenorrhoea The uterus was slightly enlarged the right ovary 4–5 cm in diameter and a typical involvement of the pouch of Douglas was present at that time During the six months treatment the right ovary diminished to almost normal size and the utero-sacral area became fibrotic and not tender

During the follow up period (12 months) no complaints apart from pronounced pain produced by bowel movement the first few months when a typical small mass was present behind the cervix She conceived January 1977 following primary sterility for 8 years

Case 3

A 24 year-old woman was admitted to this hospital in December 1975 with subacute lower abdominal complaints preceded by dyspareunia and vague lower abdominal pain for some months At laparotomy the right ovary was normal apart from endometriotic foci The left ovary as enlarged (diameter 8 cm) with endometriotic foci The uterus was normal The left ovary the abdominal part of the left tube and the rectum formed a dense partially fibrotic plate of endometriotic tissue invading the rectal wall which was almost frozen to the osseous pelvis The abdomen was closed taking into consideration the fact that the patient had no actual intestinal complaints

Treatment with Danazol was started immediately and the pains disappeared quickly Six weeks later the mass on the left side had diminished considerably and the tenderness had disappeared When the treatment was withdrawn the pelvic organs were normal by vaginal examination apart from tiny fibrotic nodules in the uterosacral region

During a follow up period of two months a tender mass diameter 4–5 cm was found in the left side Moderate lower abdominal pains were still present but no other intestinal symptoms Treatment by Danazol was resumed and in the ensuing month the mass definitely reduced in size and was no longer tender No other complaints were elicited

Treatment by Danazol is continuing

Case 4

A 22 year old woman had a leftsided [illegible] oophorectomy due to endometriosis in 19[illegible] [illegible] followed by treatment with a variety of hormonal [illegible]tions

Referred to this hospital in 1974 because of [illegible] *rectal bleeding for 18 months* she presented with [illegible] abdominal pain and dysmenorrhoea. The recto-[illegible] septum and the retrouterine pouch showed a tender [illegible]tially fibrotic infiltration with the rectal wall [illegible] mass By proctoscopy an area with polyps was found [illegible] the biopsy showed atypical polyps probably endo[illegible]sis

Further attempts with other hormonal treatment [illegible]

In March 1976 treatment with Danazol was started [illegible] patient had at that time a mass behind the uterus about [illegible] cm in diameter which probably included the right [illegible] Four weeks later the pains and the rectal bleeding disappeared the bowel function being perfect and the mass no longer tender When treatment [illegible] Danazol was withdrawn in October 1976 the uterus [illegible] retroverted with small gritty areas in the pouch of [illegible] and slightly fibrotic utero-sacral ligaments

Follow up (6 months) No complaints The vaginal examination as mentioned above

Case 5

A 36-year old woman was admitted to this hospital [illegible] complaints of secondary infertility and dysmenorrhoea [illegible] Due to cornual occlusion an implantation of the tubes [illegible] performed The tissue removed showed an inflam[illegible] reaction and no signs of endometriosis

In 1971 a right sided hemicolectomy due to endo[illegible]sis of the caecum was performed After this the [illegible] was followed in the out patient department of this [illegible] complaining of menorrhagia dysmenorrhoea dyspar[illegible]unia secondary infertility and persistent bowel [illegible] (three motions a day) Hormonal treatment of [illegible] types failed

When treatment by Danazol was started in [illegible] 1975 the ovaries were about 8 cm in diameter and the uterus slightly enlarged After a few weeks the [illegible] *tenderness disappeared* When treatment wa[illegible] [illegible]tinued after six months the ovaries were normal

During a follow up period of 11 months there [illegible] complaints the periods being normal with no dys[illegible]rhoea Dyspareunia was not reported and the patient had two normal bowel movements a day The uterus and the ovaries were normal but a minimal amount of fibrotic tissue remained behind the cervix

Case 6

A 30-year old woman had a laparotomy [illegible] (performed elsewhere) which showed the right ovary con[illegible]taining a haemorrhagic (follicular) cyst which [illegible] moved The left ovary was *normal* On the caecum [illegible] could be seen an endometriotic nodule (diameter [illegible]

In 1975 a second laparotomy (performed elsewhere) showed the left ovary to be cystic due to endometriosis and this was resected Disseminated endometriotic [illegible] *were observed* on the pelvic peritoneum The [illegible]



? (a) *Uterine endometrium and adenomyosis* Con discrepancy between the epithelium the glands ne stroma of the endometrium and of the adenomyo- ×25) (b) *Endometrium* Moderate atrophy ilatation of the glands rather flat epithelium and ution of the stroma with fibrosis and very few vessels (high power ×250) (c) *Adenomyosis* Almost normal follicular phase with straight glands tall epithelium proliferating glands and numerous vessels (high power ×?50) (H Søgaard The University Institute of Pathology Aarhus)

ly adherent to the left uterine margin and showed an ıng endometriotic mass which included the rectal

with Danazol was started in June 1976 when included lower abdominal pain together with produced by bowel motion and dyspareunia Vaginal on showed the uterus itself to be normal but with tended tender mass between the uterus and the rec

wing two months of treatment the mass had re sed considerably no tenderness and almost no pain asted After five months of treatment (November) no symptoms were reported and the mass was now ll fibrotic and not tender
ollow-up (5 months) Slight lower abdominal pain The t ovary 3–4 cm not tender No treatment necessary at moment

RESULTS AND DISCUSSION

The role of Danazol in the treatment of gynaecological disease is still the subject of continuing re search Thus far convincing preliminary results have been reported mainly in endometriosis (3 5 6 8) but even in this condition the indications for treatment are not fully defined

The results from the treatment of endometriosis with Danazol are apparently dependent on the dose and duration of treatment As far as the former is concerned doses of 100–800 mg daily have been used The extent of this disease and the symp tomatology should be used as an initial guide but the deciding factor must be the clinical response as

measured by the symptomatic improvement and the reaction of the endometriotic process At the same time attention must be paid to the type and degree of side effects although these are always mild (3 8) The object of treatment should be a regression of the disease process to such an extent that permanent cure is obtained

In the small series presented a daily dose of 400 mg was used representing an average of the doses used in the reports previously available The duration of the treatment was six months although published studies have reported treatment periods of between three and twenty one months

The initial results were generally satisfactory All six were relieved of pain in two to four weeks A patient presenting a history of rectal bleeding for 4 years (case 4) was cured from this symptom in four weeks The endometriotic masses regressed quickly and tenderness disappeared After three months (case 1) five months (case 6) and six months (cases 2 3 4 5) the extrauterine process had regressed to a very moderate or insignificant amount of scar tissue with no tenderness

It should be noticed that Danazol did not suppress the adenomyosis (Fig 2) occurring in case 1 in spite of the excellent response to treatment in the endometrium and the extrauterine mass A similar observation was published by Lauersen et al (8)

Side effects were mainly an increase in weight of one to six kg with or without clinical oedema Two cases had a fairly normal menstrual bleeding a few weeks after treatment was started and while episodes of vaginal staining spotting or slight bleeding at irregular intervals during treatment may be recorded as a side effect this was only a major complaint in one patient (case 1) Hot flushes dizziness and skin oiliness occurred as a minor temporary complaint in one case

So far the initial results from treatment with Danazol in genital endometriosis outside the uterus and in endometriosis involving the bowel to a varying extent were satisfactory bearing in mind that the series included cases persisting following surgery and cases treated by various steroids before Danazol was employed

The crux of the matter is the long term [illegible] and so the patients must be followed for a [illegible] of years The extent to which treatment [illegible] Danazol is able to eliminate active disease [illegible] to be seen The literature presents little evidence about the course of the disease following [illegible] of Danazol treatment (2)

The preliminary results from a [illegible] follow up indicate that further treatment [illegible] necessary for some and probably all cases [illegible] treatment may be used intermittently or [illegible] less permanently aiming at the lowest [illegible] Danazol producing the desired effect

It may be concluded that Danazol is [illegible] suppress the symptoms produced by [illegible] endometriosis and to induce an inactive phase [illegible] endometriotic tissue in the uterine append[illegible] serosa and the bowel The demand for [illegible] treatment of such cases is the subject of [illegible] clinical research in several centres

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ESTRIOL CONCENTRATIONS IN URINE AND SERUM IN PATIENTS WITH VARIOUS INTESTINAL DISEASES

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ract Pregnant women with ulcerative colitis shows uently low estriol values in both serum and urine 18 ents with ulcerative colitis 4 patients with mb Crohn 3 patients with a by pass operation were examined estriol concentrations were seen only in the patients ulcerative colitis especially in patients where an ation has been performed In one patient with severe rhea the estriol concentration in serum was low until intestinal function normalised and the estriol concen on went up exactly when the diarrhea stopped How no unequivocal connection between low estriol con tions and diarrhea could be demonstrated

have several times observed that pregnant with ulcerative colitis frequently have low ol values during an otherwise uneventful preg cy and we have therefore found it adequate to mine a group of pregnant women with various stinal diseases particularly in view of the fact as far as we know no such study has so far n published

MATERIALS AND METHODS

ts The study involves 25 patients admitted to the during the period 1974–76 We have an average of seven urine analyses and four analyses per patient and Table I is showing the on of the patient material

figures in brackets indicate the number of patients ndividual groups who had several successive urine nol secretions falling below the lower limit of the erence area (M – 2 S D) All patients with mb Crohn d by-pass operations showed normal estriol values spite of the fact that one of the patients with by pass eration had diarrhea during her pregnancy

Table II gives a more specified account of the 18 pa nts with ulcerative colitis By the term "low estriol" is ant estriol concentrations in serum and urine below the wer limit of the reference area

Group A comprises five non-operated patients with low concentrations of estriol in urine and serum Four of the patients had placental insufficiency which was ascertained both on the basis of determinations of the placental lactogen hormone (hPL) and of the children being all "small for date" (1 300–2 790 g) The last patient in this group had periods with diarrhea and also periods of normal stools during her pregnancy This patient revealed normal hPL-concentrations all the time and this case will be discussed later on

Group B consists of seven non-operated patients with normal estriol concentrations in both urine and serum and they also had normal hPL concentrations in the serum One of the patients had diarrhea during her pregnancy while the remaining six patients had normal stools All the patients delivered normal babies on time and the weight of the babies was normal

Group C contains the six operated patients four of whom had ileostomy one patient hemicolectomy and one ileorectal anastomosis The last mentioned patient had loose stools four or five times daily while the hemicolectomy patient had pulpy stools twice daily per anum None of the patients had mucous or blood stools All patients in this group revealed normal hPL-concentrations in serum but low estriol concentrations in serum and urine All delivered normal babies (3 380–3 800 g) on time Fig 1 shows the urinary estriol concentrations in group C as compared with group B

Methods Urinary estriol was measured by a colorimetric method described by Aasted Frandsen (1) Estriol concentrations in serum was measured by a radioimmunoassay using 125 iodine The method will be described in detail elsewhere (2) Placental lactogen hormone (hPL) was estimated in serum samples by an immunoelectrophoretic method described by Nørgaard Pedersen & Gaede (4)

RESULTS

In the patients with mb Crohn or by pass operation we observed normal estriol concentrations both in serum and urine Of 18 patients with ulcerative colitis four had placental insufficiency estimated on the basis of low hPL-concentrations in serum and

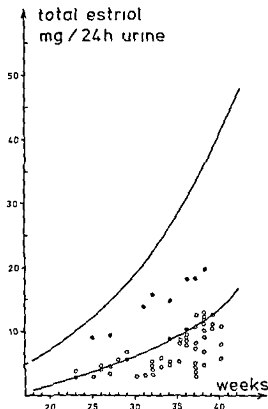


Fig 1 The urinary estriol secretion in patients with ulcerative colitis The open circles show the estriol values in six operated patients (group C) while the black circles indicate the estriol values in seven non operated patients (group B)

small for date children Of the remaining 14 patients seven had low estriol concentrations in both serum and urine Six of these patients had been operated as described under group C in Materials while the last patient had periods of both low and normal estriol values as shown in Fig 2 It is interesting to notice that in this patient the estriol concentration went up exactly at the same time as the intestinal function normalised and the diarrhea stopped

On the other hand two of the patients with normal estriol values had periods of violent diarrhea and

Table I *The distribution of the patient material*

The figures in brackets indicate the number of patients with low estriol excretion in urine

	No operation	Operation
Ulcerative colitis	12 (5)	6 (6)
Mb Crohn	3 (0)	1 (0)
By pass operation	0	3 (0)

Table II *The distribution of the 18 patients with ulcerative colitis*

The term low estriol means estriol concentrations in serum and urine below the lower limit of the reference area

	No operation		Operation	
	Low estriol	Normal estriol	Low estriol	Normal estriol
Number of patients	5	7	6	0
Group	A	B	C	D

thus there seems to be no unequivocal connection between low estriol concentrations and diarrhea in these patients It should be added that none of the patients with low estriol values received medicamental treatment

DISCUSSION

The six operated ulcerative colitis patients with low estriol concentrations had all had a large part of

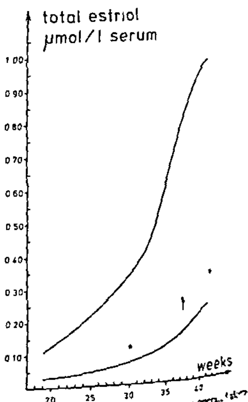


Fig 2 The estriol concentration in a non-operated ulcerative colitis patient showing a clear increase in estriol concentration at the same time as the patient's diarrhea spontaneously stopped (at the arrow)

n removed No part of the colon had been re ed from the three by pass operated patients the operated patient with mb Crohn had only 5-8 cm of her colon removed—corresponding ie proximal part Thus particularly patients a large part of colon removed seem to reveal estriol concentrations in serum and urine h may be due to a failure in the resorption of

In this connection it should be added that tin et al (3) observed that two out of three icillin treated pregnant women showed a lower entration of estriol in the urine during the od of treatment than before This the authors lain is caused by an interruption of the bacterial onjugation of estriol glucuronide which means this compound is excreted in the faeces

i one non-operated patient (Fig 2) is seen a r connection between the patient s estriol con tration in serum and urine and her diarrhea e normalizing of her intestinal function gave a ent increase in the estriol concentration Strong rhea may thus in some patients give low estriol values in serum and urine while in other patients we have seen normal estriol values even in periods of strong diarrheas Furthermore it is noticed that the hPL-concentration in serum is completely inde pendent of both intestinal function and operation

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TREATMENT OF CLIMACTERIC AND POSTMENOPAUSAL WOMEN WITH 17 β OESTRADIOL AND NORETHISTERONE ACETATE

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stract Thirty four climacteric and 175 postmenopausal men were treated with three different preparations con ning microcrystalline 17β oestradiol and norethisterone tate for climacteric symptoms and symptoms of strogen deficiency 56 of the women (mean age 5?±5 ? ars) were treated with trisekvens® (Group I) 131 wo- n (mean age 53±6 3 years) with trisekvens® forte roup II) and 2 women (mean age 55 3±5 2 years) with rofem® forte (Group III) The patients were followed ½–3½ years All patients were subjected to a general d a gynaecological examination Two or more serum mples were obtained from 145 of the patients during the atment Laboratory investigations included Auto- emis ® analysis of serum levels of triglycerides olesterol Ca Na K+ alkaline phosphatase eatinine glucose protein albumin haptoglobin zinc lphate Fe TIBC bilirubin ALAT and ASAT and dioimmunoassay of serum levels of FSH LH and low lar oestrogens (LPE)

S-cholesterol levels fell during the treatment in all three oups and in patients with elevated *S-cholesterol levels* e values were reverted to normal after 6 months treat nt There was no change in S triglycerides except in oup I where a slight increase (*P*<0 01) was observed ?4 *mon hs treatment* There were no other changes the values obtained from the Autochemist® analysis levels of FSH and LH decreased during the treat and this decrease was more pronounced in groups II III *Serum LPF* levels increased in group I for imacteric women to values *observed during a normal* phase and in postmenopausal women to values during the proliferative phase In groups II and III serum LPE values in postmenopausal women in to levels corresponding to the luteal phase Large ndividual variations in serum LPE levels were observed even during a *rigorously* standardized tablet intake which might be explained by individual differences in absorp- tion

The therapy resulted in a disappearance of the climacteric symptoms (vasomotor symptoms nervous ness irritability and sleep disturbances) and a considera ble improvement *of the* symptoms caused by oestrogen deficiency (atrophic changes in the vulva the vaginal mu cosa urethra and bladder and the state of the skin and skeletal mineral depots) Few side effects were observed 34 of the patients discontinued their treatment with the oestrogen preparations 14 changed to another type of oestrogen and 20 stopped completely 2 of them due to the discovery of mammary carcinoma In general the oestrog n preparations tested were well tolerated The oestrogen dose used in trisekvens® forte and estrofem® forte seems to be sufficient for an adequate oestrogen replacement therapy in climacteric and postmenopausal women

The climacteric is a long part of a woman s life and can last over 20 years The reduction in oestrogen output which takes place during this period leads to a decrease in all oestrogen-dependent functions Over the years a gradual diminution of the amount of follicles in the ovaries takes place and at last only a few primordial follicles and differentiated follicles remain An earlier well functioning interaction be tween the hypothalamus the pituitary and the ovaries is disturbed by the decreasing ability of the ovaries to respond to gonadotropic stimulation Af ter the menopause there is an increased production of FSH and LH from the pituitary caused by the lack of a negative feedback of oestrogens upon the hypothalamus This increase in pituitary gonadotropin production starts even before the ces sation of the ovulatory function (1)

The ovaries of women more than two years after the menopause secrete insignificant quantities of oestrogens but substantial amounts of androgens Oestrone becomes the major circulating oestrogen and arises almost entirely from the peripheral con version of androstenedione (for a review see 11) The levels of 17β-oestradiol oestrone and oestrone sulphate in peripheral blood from postmenopausal women are even lower than in males of correspond

ing age (9) This dramatic reduction in oestrogen brings about somatic as well as psychological troubles which however in many cases can be cured or improved by oestrogen replacement therapy

The symptoms appearing during the climacteric and postmenopausally can be divided into two groups The first group includes *climacteric symptoms* depending upon hormonal disturbance Irregular uterine bleeding Vasomotoric symptoms (e g hot flushes sweats and tachycardia Nervousness irritability insomnia and *depression* The second group consists of *symptoms caused by the cessation of oestrogen production* and which may be regarded as symptoms of oestrogen deficiency Atrophy of the vulva Atrophy of the vaginal mucosa Atrophic changes in the urethra and bladder causing disposition to urethritis cystitis and urge incontinence and also stress incontinence caused by atrophic changes in the surrounding tissues Thinning of the skin due to epidermal atrophy and reduced mitosis Osteoporosis and Changes in blood lipids

Hormonal Therapy

Oestrogen therapy has been used since the 1930s Irregular uterine bleeding during the climacteric depends upon the effect of unopposed oestrogens on the endometrium causing prolonged withdrawal bleeding Administration of progestagens transforms the endometrium to a secretory phase When oestrogen production decreases the administration of progestagens has no effect and then oestrogen treatment can be added The vasomotor symptoms appear as a result of adequate oestrogen therapy

There has been much discussion as to whether rvousness irritability and depression appear as a result of hormonal disturbance during the climacteric Other factors probably play a part in the development of such symptoms Between the ages 50 and 60 years a woman s life often changes course The climacteric can be considered as a time of losses and women have feelings of inadequacy which can be the cause of the psychological symptoms nevertheless improvement of psychological symptoms as a result of oestrogen treatment have been reported (8 13 14)

The symptoms caused by cessation of the oestrogen production show a clearly positive response to oestrogen replacement therapy A striking effect is observed upon the mucosa of the vagina urehtra and bladder neck Long standing urethritis and cystitis disappear followin[illegible] adequate oestrogen therapy Oestro[illegible] tionably influence the skin by inducing [illegible] water retention stimulating hyaluronidase [illegible] and improving skin circulation (? 1? 25)

Concerning osteoporosis oestrogen therap[illegible] lays and prevents bone loss in postm[illegible] women (10 23)

The influence of oestrogens upon blood [illegible] been frequently discussed Synthetic oestro[illegible] fluence the *lipid metabolism in several* wa[illegible] ethinyl oestradiol increases the con[illegible] triglycerides and decreases the concentra[illegible] antithrombin III (6) and changes the levels of [illegible] lation factors VIII IX and X (4) The e[illegible] so-called natural oestrogens on the lipid metab[illegible] is different in this respect they decrease the [illegible] lipid levels (18) and in addition Åstedt & J[illegible] (28) demonstrated that they do not red[illegible] fibrinolytic activity in the venous wall wh[illegible] case when synthetic oestrogens are used It [illegible] therefore be preferable to use natural oestrogens [illegible] the replacement therapy in climacteric and p[illegible] menopausal women There is however a ne[illegible] more controlled studies on the influence of [illegible] types of oestrogens in different dose levels up[illegible] postmenopausal lipid and lipoprotein metabol[illegible]

The following types of oestrogens have be[illegible] established in Scandinavia for replacement th[illegible] Synthetic steroid oestrogens (ethinyl oe[illegible] and mestranol) Esterified natural oest[illegible] (17β oestradiol valerate) Conjugated natural [illegible] trogens (mainly oestrone sulphate) and synthe[illegible] nonsteroidal oestrogens (diethylstilboestrol) Ea[illegible] ier attempts to use free natural oestroge[illegible] oestradiol) in *oral preparations* proved uns[illegible] ful mainly due to poor absorption however 1[illegible] oestradiol in its micronized form has been sh[illegible] be active when taken orally (17 21) Lebe[illegible] demonstrated that oral administration of [illegible] oestradiol+0 5 mg of oestriol to postmeno[illegible] women increased the plasma 17β-oestradiol le[illegible] to values comparable to those seen in the [illegible] phase Yen and co-workers (?7) meas[illegible] red the se[illegible] rum levels of oestrone *17β-oestradiol* FSH [illegible] LH after intake of one single tablet conta[illegible] of micronized 17β oestradiol The levels of LH [illegible] FSH were significantly decreased within 3 [illegible] hours respectively and both gonadotrop[illegible] mained suppressed for 24 hours after the [illegible] The level of oestrone reached a peak value [illegible]

ınding to a ?000 % increase after 6 hours and the el of 17β-oestradıol reached a maximum after 5 ırs and remained significantly elevated 8 hours r tablet intake These experiments clearly indı e that micronized 17β oestradiol is readily ab bed and that a significant fraction of the hor ne is converted to oestrone

ontinuous treatment with oestrogens is not suit e because it leads to a hyperplasia of the en netrium which sometimes can be difficult to dis guish from an early endometrial cancer strogen administration should therefore be lic—or better combined with progestagen rapy in the second half of the cycle Pro- tagens modifies the stimulatory effect on the ast of continuous oestrogen administration gestagen administration given at regular inter s in oestrogen treated patients transforms the lometrium to a secretory phase prevents atypia the nuclei and brings about withdrawal bleeding) The present communication describes the clin trials of a recently developed oestrogen replace nt preparation containing micronized 17β tradiol and oestriol with the addition during second half of the treatment cycle of rethisterone acetate as the progestagen isekvens® NOVO Industri AB Malmo Swe n)

Abbreviations and Trivial Names

olesterol 5 cholesten 3β ol Diethyl stilboestrol -di(p-hydroxyphenyl) 1 2 diethyl ethylene Eth l oestradiol 17α ethinyl 1 3 5 (10) oestratriene 7β-diol FSH Follicle stimulating hormone L Luteinizing hormone LPE Low polar oes gens (synonym immunoreactive oestrogens 17β stradiol + oestrone) Mestranol 3 metoxy 17α inyl 1 3 5 (10)-oestratrien 17β ol Norethister e acetate 17β acetoxy 17α ethinyl-4 oestren 3 e 17β-oestradiol 1 3 5 (10)-oestratrien 3 17β ol Oestriol 1 3 5 (10) oestratrien 3 16α 17β ol Oestrone 3 hydroxy 1 3 5 (10) oestratrien rone Oestrone sulphate 3 sulphoxy 1 3 5 (10) stratrien 17 one Progesterone 4 pregnene 3 20- one

MATERIAL AND METHODS

Pharmaceutical Preparations

ree kinds of oestrogen preparations were used in the lowing dose regimens

(1) *Trisekvens®*
- 12 tablets with 2 mg of 17β oestradiol and 1 mg of oestriol
- 10 tablets with 2 mg of 17β oestradiol 1 mg of oestriol and 1 mg of norethisterone acetate
- 6 tablets with 1 mg of 17β oestradiol and 0 5 mg of oestriol

(2) *Trisekvens® forte*
- 1? tablets with 4 mg of 17β-oestradiol and 2 mg of oestriol
- 10 tablets with 4 mg of 17β oestradiol 2 mg of oestriol and 1 mg of norethisterone acetate
- 6 tablets with 1 mg of 17β oestradiol and 0 5 mg of oestriol

(3) *Estrofem® forte*
- 28 tablets with 4 mg of 17β oestradiol and 2 mg of oestriol

Clinical Material

The investigation included 209 women who have been followed during 2 5–3 5 years The clinical material was divided into three groups

Group I Trisekvens® 56 women aged 46–64 years (mean 5_±5 ?) of which 27 were menopausal The remain ing 29 were still menstruating but had irregular menses and climacteric symptoms such as sweats hot flushes tachycardia and depression

Group II Trisekvens® forte 131 women aged 47–69 years (mean 53±6 3) All of this group were menopausal except 7 who still menstruated and 3 who suffered from primary amenorrhoea

Group III Estrofem® forte 2_ women aged 49–68 years (mean 55 3±5 2) all menopausal and all of them had undergone hysterectomy before the treatment started

Before the medication started all women had a general and gynaecological examination vaginal smears were taken and their breasts were examined The patients were re examined once a year Serum samples were taken prior to treatment and it was intended to repeat this sampling after 6 12 18 and 24 months of treatment It was not possible to obtain serum samples from all patients on every occasion Samples were obtained from 145 patients (69 3%) twice or more during the period of treatment 3? in group I 95 in group II and 18 in group III All tests were made on fasting samples

General Clinical Chemical Analysis

S-Cholesterol (24) S triglycerides (?6) S Ca S K+ S Na+ S alkaline phosphatase S Creatinine S-Glucose S Protein S Albumin S Haptoglobin S Zink sulphate S Fe S TIBC S Bilirubin S Alanine aminotransferase (S ALAT) and S Aspartate aminotranferase (S ASAT) were determined in an Autochemist® automatic analyser at the department of clinical chemistry St Erik s Hospital Stockholm

Hormone Analyses

The hormone assays were carried out at the hormone laboratory Sabbatsberg Hospital S-LPE (low polar

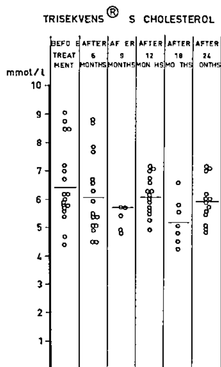


Fig 1 S cholesterol levels following treatment with Trisekvens®

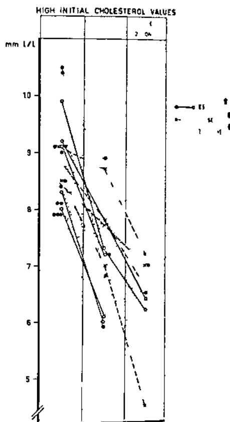


Fig 2 Effect of oestrogen therapy upon S-cholesterol levels in patients with high initial values

oestrogens) were determined by the radioimmunoassay technique of Edqvist & Johansson (5) using an antiserum against 17β-oestradiol hemisuccinate bovine serum albumin (22) This antibody reacts to 100% with 17β oestradiol and to 50% with oestrone (20) and the values are expressed as pmol immunoreactive 17β oestradiol equivalents per litre S FSH and S LH were determined radioimmunologically using DASP® separation (Organon Oss Holland) Antisera against FSH and LH and purified FSH and LH for ^{125}I labelling were from KABI AB Stockholm Sweden The values expressed in units per litre serum of Human Pituitary FSH 68/39 and Human Pituitary LH or ICSH 68/40 respectively

RESULTS

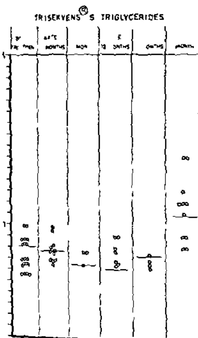
With the exception of S cholesterol and S triglycerides no changes were noted in the values from the general clinical chemical analyses during the treatment An account will therefore be given only for the values of S cholesterol S triglycerides S FSH S LH and S LPE

Group I Trisekvens®

The values for S cholesterol were normal before treatment except in 4 cases who had elevated levels (Fig 1) The high values fell rapidly to normal levels during treatment (Fig 2) All other values remained normal during the treatment After 24 months a slight decrease was noted ($P<0.05$)

The levels of S triglycerides were normal in all cases (Fig 3) and underwent no changes up to 18 months of treatment A slight increase ($P<0.0$…) was observed after 24 months

The levels of FSH and LH decreased ($P<0$…) and LPE increased ($P<0.01$) during the treatment (Figs 4 and 5) There were differences between the menopausal patients and those who were still menstruating when considering the hormone levels The latter group showed higher LPE values than the menopausal patients (Fig 5) During the treatment LPE values in the climacteric group corresponded to those found during the luteal phase in a normal menstrual cycle while the values found for the menopausal group corresponded to follicular phase levels FSH and LH decreased in both groups but not to values found during the reproductive phase of life



3 S-Triglyceride levels following treatment with ekvens®

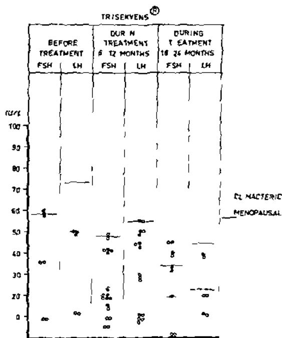


Fig 4 Serum levels of FSH and LH following treatment with Trisekvens®

up II Trisekvens® forte

re is a statistically significant ($P<0\ 001$) de ise in S-cholesterol levels after 12 and 24 months reatment (Fig 6) Those patients who had ele d cholesterol values developed normal levels r 6 months of treatment (Fig 2) S triglycerides wed no significant change during the treatment 7)

SH and LH decreased ($P<0\ 001$) during the ent (Fig 8) and this decrease was more pro- nced than that following treatment with tens® LPE increased ($P<0\ 001$) to values to those found during the secretory the menstrual cycle (Fig 9)

up III Estrofem® forte

a statistically significant ($P<0\ 001$) de in S-cholesterol levels after 12 months of ment (Fig 10) As in group II cholesterol val 10 patients with elevated levels prior to treat t decreased to normal after 6 months of treat t (Fig 3)

here was no significant changes in S tri cerides (Fig 11)

SH and LH decreased ($P<0\ 001$ and $P<0\ 01$ ectively) during treatment (Fig 12) LPE in ased to values corresponding to those found

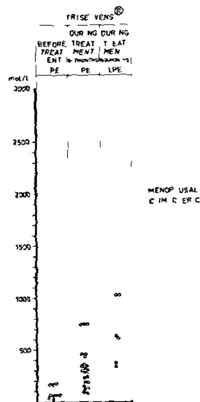


Fig 5 Serum levels of LPE following treatment with Trisekvens®

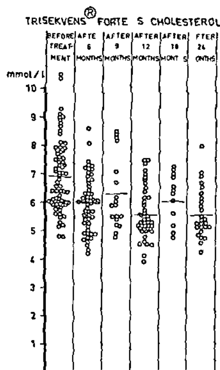


Fig 6 S Cholesterol levels following treatment with Trisekvens® forte

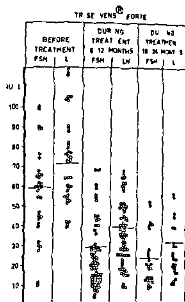


Fig 8 Serum levels of FSH and LH following treatment with Trisekvens® forte

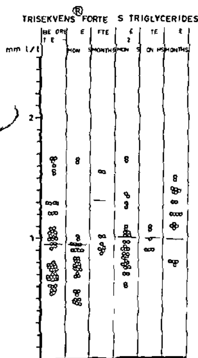


Fig 7 S Triglyceride levels following treatment with Trisekvens® forte

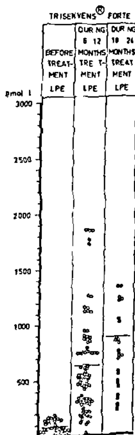
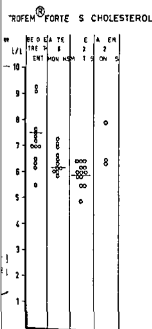


Fig 9 Serum levels of LPE following treatment with Trisekvens® forte



10 S-Cholesterol levels following treatment with trofem® forte

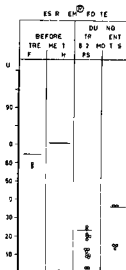
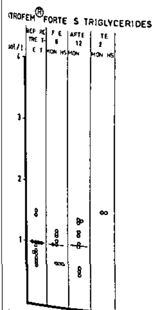


Fig 12 Serum levels of FSH and LH following treatment with Estrofem® forte



ig 11 S-Triglyceride levels following treatment with strofem® forte

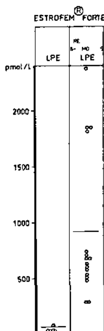


Fig 13 Serum levels of LPE following treatment with Estrofem® forte

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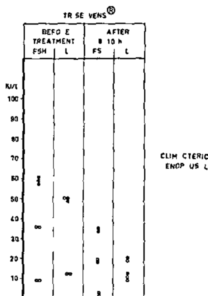


Fig 14 Serum levels of FSH and LH 8–10 hours after intake of one single tablet of Trisekvens®

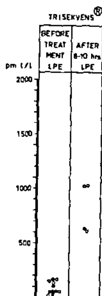


Fig 15 Serum levels of LPE 8–10 hours after intake of one single tablet of Trisekvens®

during the luteal phase of a normal menstrual cycle (Fig 13)

We noticed that the hormone values during the treatment were very variable 42 patients therefore underwent a controlled investigation They were instructed to take a hormone tablet which contained only oestrogens 8 hours before the hormone determination The results are listed in Figs 14–17 It is noted that the values still differ considerably from each other which may depend upon large individual differences in absorption

Influence upon Climacteric Symptoms

Treatment of patients having irregular menstruation with trisekvens® resulted in a regulation of their cycle

The vasomotor symptoms disappeared after a few days medication The patients were able to sleep better than before and in many cases stopped their intake of hypnotic drugs

Using psychological tests Fedor Freybergh (7) has demonstrated that treatment of climacteric and postmenopausal women with 17β oestradiol valerate (Progynon®) had a positive effect upon depression performance concentration and memory disturbances No systematic psychological tests have been applied in the present study but most patients claimed positive effects upon depression nervousness performance memory and concentration

Influence upon Symptoms of Oestrogen Deficiency

In all cases atrophy of the vulva and of the vaginal mucosa ceased following oestrogen treatment and a positive effect was also found on senile ... Patients who had been suffering from recurrent cystitis and urethritis improved considerably during treatment with trisekvens® forte and estr... forte Positive effects were also noted upon the skin

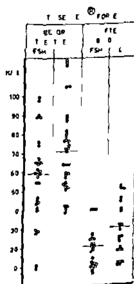
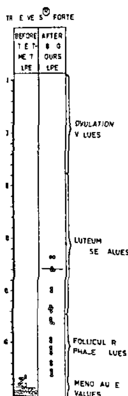


Fig 16 Serum levels of FSH and LH 8–10 hours after intake of one single tablet of Trisekvens® forte



17 Serum levels of LPE 8–10 hours after intake of single tablet of Trisekvens® forte

swollen and sore finger joints frequently seen in stmenopausal women improved considerably ring treatment with trisekvens® forte and rofem® forte

Together with Dahlen Jacobson & Lamke (3) we died the effect of trisekvens® forte and trofem® forte on the physiological bone loss in 13 tients receiving oestrogen and in 13 controls It s found that the skeletal mineral depots in eased significantly in the hormone treated group th an average of 6% during a one year follow up riod There was no correlation between bone neral change and the age of the patient

As previously shown cholesterol values de eased during oestrogen treatment while the levels triglycerides remained unchanged

Side Effects

ractically no side effects were observed in the 145 atients from which two or more serum samples ere obtained No nausea and vomiting was bserved Mastodynia appeared in 12% of the patients at the beginning of the treatment but disappeared after 2 months Irregular uterine bleeding due to irregular tablet intake occurred in 6 patients A curettage was performed in all these cases and revealed no malignancy 6 patients using trisekvens® forte suffered from copious withdrawal bleeding and the medication was changed to estrofem® forte for 28 days followed by a tablet free week Four patients suffered from premenstrual and menstrual pain during treatment with trisekvens® forte and these patients also changed to estrofem® forte for 28 days followed by one tablet free week

Of the remaining 64 patients receiving the NOVO tablets and from whom we obtained less than two serum samples 34 stopped the medication for the following reasons Fourteen women changed to another type of oestrogen One of them wanted to have injections instead of taking pills 7 women went to other doctors who prescribed conjugated oestrogens (Premarin®) or 17β-estradiol valerate (Progynon®) instead of trisekvens® 2 women developed oedema and 4 complained of copious withdrawal bleeding In these cases 2 mg of 17β-oestradiol valerate (Progynon®) daily was prescribed

Twenty patients completely stopped their hormone medication Two patients in this group had hypertension (190/100 and 160/90 respectively) Hereditary factors might have been involved as their parents had also been hypertensive They went to their general physician who declared that oestrogen medication was dangerous for them and they therefore stopped the medication One patient did not like to take tablets every day 2 became oedematous and gained weight one suffered from nausea 2 did not like to menstruate and one patient stopped because she read in a newspaper that oestrogens could provoke cancer One patient who suffered from depression did not improve during treatment with trisekvens® forte and 8 patients did not return for re-examination after one year

Two patients developed a mammary carcinoma which was found during the check up One was a 52 year-old woman who had last menstruated 6 months previously and was treated cyclically with conjugated oestrogens (Premarin®) and 1 5 mg of allyloestrenol (Gestanyn®) One year later a lump was found in her breast and biopsy revealed a medium–well differentiated macrocytic ductal cancer She received immediate surgical treatment

The other cancer case was a 57 year old woman who had been treated with trisekvens® forte for 1 5 years Her cancer was small and without metastases and no postoperative treatment was carried out Both patients are now doing well According to Kupperman (15) the expected frequency of breast cancer in the age group 50–60 is 5 cases per 100 women The present study include 2 cases in 200 oestrogen treated women During the same period of time we found 3 cases of breast cancer among the patients who had not been treated with oestrogens

DISCUSSION

The treatment of climacteric and postmenopausal women with trisekvens® trisekvens® forte and estrofem® forte considerably improved their general condition and relieved their climacteric symptoms Few side effects were observed Fibromas have been reported to increase in size during oestrogen treatment although this occurs very rarely Patients with small fibromas were included in the present study but in no case was growth of the tumour observed It is also worth mentioning that no changes in the blood electrolytes or liver enzymes were observed during the treatment

According to Lauritzen (1973) the dose of oestrogen used in replacement therapy should always be individualized according to the need of the patient and the lowest maintenance dose should be administered From a practical point of view however such individualized doses are difficult to determine

The patients taking trisekvens® showed higher H and LH levels during the treatment than those ing trisekvens® forte or estrofem® forte Furthermore patients taking trisekvens® showed a tendency to higher blood levels of triglycerides after 2 years of intake The dose of oestrogen in trisekvens® may be insufficient to prevent the rise in blood triglyceride levels which develops after the menopause and it also exerts a less pronounced suppressive effect upon the hypothalamic–pituitary axis especially in menopausal women The mean levels for serum LPE in menopausal subjects during trisekvens® treatment corresponded to those found in the proliferative phase of a normal menstrual cycle

Treatment with trisekvens® forte and estrofem® forte resulted in a more pronounced suppression of the FSH and LH levels Serum triglycerides remained unchanged during this treatment, but [illegible] cholesterol levels were significantly [illegible] High cholesterol levels fell to normal values [illegible] treatment with trisekvens® forte and e[illegible] forte as well as with trisekvens® The serum LPE levels in menopausal subjects during treatment with trisekvens® forte and estrofem® f[illegible] responded to those found in the luteal phase of a normal menstrual cycle

Trisekvens® forte and estrofem® forte seem [illegible] be sufficient for the prevention of the [illegible] changes associated with postmenopausal oe[illegible] deficiency while trisekvens® in some cases [illegible] effective in this respect Referring to the de[illegible] ment of osteoporosis only trisekvens® f[illegible] estrofem® forte were tested and treatment [illegible] these preparations resulted in a significa[illegible] in the bone mineral reserve

It can be concluded from the above dis[illegible] that oestrogens for replacement therapy sh[illegible] given in doses which give rise to serum LPE le[illegible] corresponding to those found during the [illegible] luteal phase

The patients should be re-examined at leas[illegible] a year In our series the patients were pres[illegible] tablets for a 3 months period and thereafter ha[illegible] report as to their general health and any s[illegible] fects before receiving a new 3 month supply

After the menopause oestrogens are s[illegible] duced for some time and many women have [illegible] climacteric symptoms Women without sy[illegible] often want to be treated with oestrogens be[illegible] they have read about the advantages of s[illegible] therapy There is sufficient evidence concern[illegible] benefits of oestrogen therapy to allow treatm[illegible] patients without climacteric symptoms

On the other hand many patients have a neg[illegible] attitude to oestrogen treatment partly due t[illegible] cles in newspapers and magazines dealing [illegible] risk of cancer In this series there were few wo[illegible] who discontinued their oestrogen medica[illegible] who never returned for new tablets This can b[illegible] depended upon the fact that the patients we[illegible] informed before treatment commenced S[illegible] tients prefer to have climacteric sympt[illegible] want to be ill to play the role of [illegible] S[illegible] patients also have an irrational fear tha[illegible] oestrogen therapy one is tampering with the [illegible] nature other women feel a sense of relief [illegible] menstruation ends They have never been [illegible] at being a woman and now at last they [illegible]

the detestable evidence of their womanhood Pa ts with a negative attitude to oestrogen medica i should not be persuaded to alter their ideas

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THE EFFECT OF VARIOUS DOSES OF ORAL OESTRADIOLVALERATE AND OESTRIOLSUCCINATE ON URINE CALCIUM/CREATININE SERUM FSH AND ENDOMETRIUM IN CASTRATED WOMEN

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tract The effects of various doses recommended for cal use of oestradiolvalerate and oestriolsuccinate on e cal ium/creatinine serum FSH and endometrium investigated in two castrated women Oestrogen tments were given in 6-week periods separated by 2 ks without treatment After various oestrogen treat ts serum FSH generally decreased clearly and urine ium/creatinine slightly The proliferative effect on en etrium was investigated histologically In no period a hyperplastic endometrium found

size of the dose in oestrogen substitution rapy is often determined by the effect on vegeta symptoms yet most of these symptoms are not y good indicators of the therapy s effectiveness ording to Lauritzen the only specific cli -ten complaints are hot flushes combined h dizziness and sweating and a paroxysmal rise blood pressure (4) The main purpose of long n oestrogen therapy is to prevent or postpone enerative post menopausal tissue changes such oesteoporosis and atrophy of skin and mucous mbranes No correlation has been found be en vegetative symptoms and cytohormonal tus or skin changes (2 7) One of the most com n side effects associated with oestrogen therapy excessive endometrial proliferation and uterine edings It has been suggested that the increased idence of endometrial carcinoma (9) may have to with the greatly increased use of oestrogens art from these effects on post menopausal tissue ang s it is important to ascertain the effect of nical oestrogen doses on the endometrium

The purpose of the study was to determine the ect of various doses of oestradiolvalerate and striolsuccinate on urinary calcium/creatinine rum FSH and endometrium

SUBJECTS AND METHODS

The subjects were 2 female patients 31 and 35 years of age Both had undergone bilateral oophorectomy 1? years previuosly for ovarian tumours but the uterus had been preserved The patients had last received oestrogen treatment about one month before the study started In the present investigation oestrogen therapy was given in 6-week periods separated by 2 weeks without treatment At the beginning and end of each treatment period the urinary calcium and calcium/creatinine and serum FSH were measured and an endometrial biopsy specimen was taken from the lateral wall of the uterine body

Urine samples were collected after an overnight fast from 8 p m the previous evening The urine wa col lected between 8 and 10 a m the overnight urine having been discarded Calcium and creatinine were estimated in urine samples by standard auto-analyzer techniques (1) Serum FSH was determined radioimmunologically (5)

RESULTS

Urine calcium and calcium/creatinine

The oestrogen doses used daily in the 6-week treatment periods and the effect of treatment on urine calcium and calcium/creatinine are presented in Figs 1 and 2

FSH

The effect of the same oestrogen treatments on serum FSH is shown in Fig 3

Effect on the endomtrium

The effect of the 6-week oestriolsuccinate therapy (2 mg/day) on the endometrium was minimal Mild signs were noticed in the glandular epithelium

The corresponding treatment with oestradiolval erate (1 mg/day) or with oestradiolvalerate 1 mg+oestriolsuccinate 2 mg/day caused weak pro-

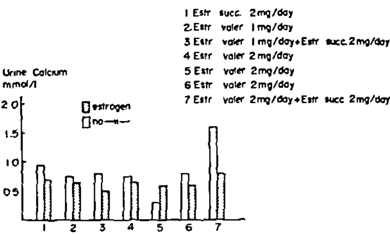


Fig 1 Urine calcium before and after [illegible] weeks of oestrogentherapy

liferation The endometrium was low and there was mild stromal proliferation A more pronounced effect of oestrogen therapy was seen with oestradiolvalerate 2 mg/day Proliferation was observed in the surface epithelium glands and stroma The 6-week treatment has been given three times separated by 2 week intervals without treatment After the 2 week interval there were mild signs from the effect of oestrogen At the end of the third treatment period the endometrial proliferation was about the same as at the end of the two previous treatment periods A fairly marked proliferation was observed when oestradiolvalerate 2 mg + oestriolsuccinate 2 mg/day were used for 6 weeks (Fig 4)

DISCUSSION

Plasma and urinary calcium are mildly elevated [illegible] postmenopausal women (8) The calcium [illegible] the premenopausal level with oestrogen therapy [illegible] Gallagher & Nordin consider that determination of the fasting urinary calcium/creatinine in addition [illegible] the urinary hydroxyproline/creatinine gives the [illegible] index of a reduction in bone resorption [illegible] regard these measurements as most useful [illegible] assessing the effect of oestrogen treatment [illegible] In this study the 6 weeks of oestrogen treatment with various doses generally led to effect was [illegible] with oestriolsuccinate 2 mg/day After a [illegible] interval there was always a slight increase [illegible] urinary calcium and calcium/creatinine [illegible]

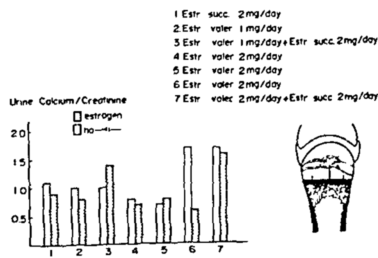




Fig 2 Urine calcium creatinine [illegible] after six weeks of oestrogentherapy

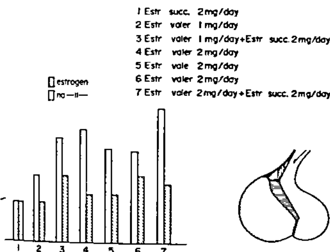




Fig 3 Serum FSH before and after six weeks of oestrogen-therapy (means of the values of two women)

hanism by which oestrogen affects the skeleton not entirely clear but its inhibiting effect on bone orption can be regarded as a blockage of the ion of parathyroid hormone on bone (1)

Oestriol has been considered to have a specific ect on vaginal and cervical epithelium (6) In s study 6 weeks of oestrogen in the glandular thelium of the endometrium In Heuser and emmler's study (3) 13–34 days of oestriolsuccate therapy (2 mg/day) caused endometrial mulation in 9 out of 11 postmenopausal women e most pronounced effect on the endometrium s observed in patients whose last menstrual riod had occurred less than one year previously rthermore daily treatment with 4–8 mg caused neralized endometrial proliferation It is thus evident that oestriol also affects the endometrium The question concerns the dosage The 6-week treatment with oestradiolvalerate (2 mg/day) was given three times with 2 week intervals without treatment No cumulative effect of oestrogen was observed At the end of the third treatment period the proliferation was about the same as at the end of the two previous treatment periods and corresponded to the middle of the proliferative phase of the normal menstrual cycle A possible factor in the etiology of endometrial carcinoma is thought to be cystic glandular hyperplasia and precancerous adenomatous hyperplasia In this study no changes consistent with hyperplasia were seen No uterine bleedings occurred during or after oestrogen treatments

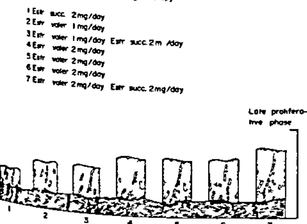


Fig 4 Endometrial thickness after six weeks of oestrogentherapy Before treatment endometrium was quite atrophic (The evaluation is based on histologic examination)

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CHANGES IN SERUM LIPIDS DURING TREATMENT WITH NORGESTREL OESTRADIOL VALERATE AND CYCLOPROGYNON®

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ract The serum concentrations of triglycerides esterol and free glycerol were determined in 23 acteric women before and after the administration of e different steroid drugs Each drug was given within a od of 12 weeks (3 cycles) Period I Norgestrel 0 5 mg from the 12th to 21st day of each cycle Period II tradiol valerate (Progynon®) 2 mg daily from the 2nd 1st day of each cycle Period III Oestradiol valerate 2 from the 1st to 11th day followed by oestradiol rate 2 mg+0 5 mg *dl* norgestrel from day 12 to 21 of cycle (Cycloprogynon®) A significant decrease in ycerides was observed following the administration of gestrel and Cycloprogynon® whereas oestradiol rate had no effect on the triglyceride levels On the r hand oestradiol valerate following a period of nor rel produced an increase *in serum cholesterol levels*

ignificant decrease in the serum concentration of lycerides has previously been demonstrated in nacteric women treated with Cycloprogynon® (2 oestradiol valerate daily from the 2nd to 11th followed by 2 mg oestradiol valerate+0 5 mg norgestrel daily from the 12th to 21st day of the le) (5) This was accompanied by a non nificant decrease in serum cholesterol free cerol and free fatty acids

The present *investigation* was carried out in order determine the drug responsible for this decrease serum lipids i e norgestrel oestradiol valerate the sequential combination of the above two

MATERIAL AND METHODS

e material consisted of 23 women between the ages of and 55 years average 45 years (S D ±4 2) They had all en referred to the Gynaecological Department of the Odense University Hospital owing to menometrorrhagia Diagnostic curettage was carried out *in order* to exclude the possibility of malignancy In addition to the above symptoms 18 of the patients complained of vasomotoric and/or other climacteric symptoms A clinical examina tion revealed no other pathological conditions

The set up of the investigation was as follows No hormonal therapy for at least 3 months prior to being admitted to the trial Two clinical examinations (including the withdrawal of blood samples) with an interval of two weeks Thereafter each patient was given firstly nor gestrel for three cycles secondly Progynon® for three cycles and thirdly Cycloprogynon® for three cycles Each cycle was 28 days

The hormones administered orally were as follows *Norgestrel 0 5 mg dl norgestrel daily from the 1 th to 21st* day of the cycle *Progynon®* 2 mg oestradiol valerate from the 2nd to 21st day of the cycle *Cycloprogynon®* 2 mg oestradiol valerate daily from the 1st to 11th day and 2 mg oestradiol valerate+0 5 mg *dl* norgestrel daily from the 12th to 21st day of the cycle

Each patient was examined between 8 and 9 a m fol lowing a minimum period of 8 hours of fasting All the examinations apart from those carried out prior to being admitted to the trial were performed on the 22nd day of the cycle i e on the morning after the patient had taken the last tablet of each treatment cycle The patients were weighed the blood pressure measured and venous blood samples withdrawn for the determination of serum triglycerides *total serum cholesterol and serum free* glycerol

The triglycerides and free glycerol were determined according to the method of Eggstein & Kreutz (8) and the cholesterol according to the method of Huang et al (9)

No attempt was made in the present investigation to evaluate the symptomatic effect of the treatment

Wilcoxon s test for paired comparison has been em ployed for the statistical evaluation of the hormonal effect on the serum lipid concentrations In thi manner each patient acted as her own control The limit of significance employed was $p<0.05$

Table I *Mean values (±S D) of serum triglycerides cholesterol and free glycerol in* [illegible] *women before and after 3 sequential periods of hormonal treatment each consisting of* [illegible] *oestradiol valerate and a combination of these (Cycloprogynon®) respectively*

	Pre treatment	Norgestrel			Oestradiol valerate			Oestradiol valerate + norgestrel		
		I	II	III	I	II	III	I	II	[illegible]
Triglyceride mM/l	1 17	0 87*	0 94	0 87*	1 00	1 10	1 18	0 96	0 91	[illegible]
S D	0 29	0 32	0 25	0 20	0 [illegible]7	0 31	0 29	0 30	[illegible]	[illegible]
Cholesterol mM/l	6 4	6 0	6 5	6 4	6 7	6 9	7 0	6 5	6 1	[illegible]
S D	1 [illegible]	1 0	1 2	1 3	1 1	1 1	1 4	1 3	1 0	[illegible]
Glycerol mM/l	0 062	0 060	0 063	0 076	0 074	0 066	0 061	0 080	0 069	[illegible]
S D	0 020	0 039	0 040	0 050	0 055	0 035	0 0[illegible]3	0 048	[illegible]	[illegible]

*=p<0 01 **=p<0 05

RESULTS

The serum concentrations of triglycerides total cholesterol and free glycerol are shown in Table I In this the mean values and standard deviations for the whole material during the pre treatment phase are compared with the results obtained in the three cycles of each of the three treatment periods

The triglyceride values were significantly lower ($p<0 01$) during treatment with norgestrel in all three cycles These gradually returned to pre treatment levels during the administration of progynon® During treatment with Cycloprogynon® the triglyceride levels again decreased significantly in all three cycles ($p<0 05$) The values during norgestrel and Cycloprogynon® periods were not mutually statistically different

The total cholesterol concentrations were found o be significantly higher during treatment with rogynon® ($p<0 05$) as compared to the pretreatment norgestrel and Cycloprogynon® periods The cholesterol values were almost similar during these three periods

No significant alterations were observed in the concentrations of free glycerol throughout the whole investigation Neither were changes seen in the weight (>±2 kg) nor in the blood pressure

DISCUSSION

The effect of the Pill on lipid metabolism has been the object of discussion and investigation for quite a number of years Thus even within the last three years four investigations have been published (4 6 10 19) together with a survey (1) on the effect of combined tablets containing synthetic oestrogens and gestagens used for [illegible] purposes Beck (1) summarizes the effect of [illegible] traceptive steroids on lipid concentrations in [illegible] mal women as follows The administration of synthetic oestrogens increase the triglyceride [illegible] nortestosterone derivatives counteract this effect [illegible] Both effects seem to be dose related The [illegible] changes in serum cholesterol concentrations [illegible] to be related to the amount of gestagen [illegible] conjunction with a synthetic oestrogen [illegible]

These studies and most of the discussion [illegible] been confined to the effects of synthetic oes[illegible] on the lipids of fertile women while little atten[illegible] has been paid to women in the menopausal phase [illegible] life The present investigation was carried out [illegible] such women in order to ascertain the effect of [illegible] genuine oestrogen oestradiol valerate and [illegible] gestrel both alone and in combination on the [illegible] levels

Some authors have observed that the eff[illegible] genuine oestrogens on the lipid metabolism [illegible] from that of the synthetic oestrogens Thus [illegible] & Borggaard (12) found that a pill [illegible] 2 mg of *17β oestradiol+1 mg* oestriol+1 mg [illegible] ethisterone given to healthy women between [illegible] ages of 21 and 30 years produced no eff[illegible] the serum triglycerides or serum phosphol[illegible] whereas a pill containing 0 05 mg of e[illegible] oestradiol+1 mg norethisterone given to the [illegible] women raised the serum lipid levels On the [illegible] hand in a later investigation (13) they found [illegible] mg oestradiol+1 mg estriol or a tablet con[illegible] twice this dosage brought about a decrease [illegible] triglycerides cholesterol and phospholipids [illegible] given to post menopausal women further [illegible]

strel® and ethinyl oestradiol raised the level of lipids Borglin & Staland (2) obtained the results but Lauritzen (11) using oestradiol or riol alone was unable to see any effect on sterol or triglyceride concentration Two investigators (15 18) found that oestradiol ate lowered the cholesterol levels but not of the triglycerides Subcutaneous oestradiol ants (75 mg) were observed to decrease the ycerides but have no effect on the choles (3)

here are many reasons why conflicting results obtained from similar clinical trials For exam here can be differences in the patient s diet the hod of administration of the drug a predisposi to diabetes (14) the age of the patient in rela to the *menopause and a number of others*

n the whole it appears that most genuine rogens lower the serum lipid levels Further synthetic oestrogens raise lipid concentrations vever the latter is well-documented in contrast he former The genuine oestrogen oestradiol rate has been employed in the present in igation and the results show that it has no ct on triglyceride values (Table I) but that it s the level of cholesterol ($p<0.05$) when given e However when given together with nor l (Cycloprogynon®) it had no influence on lesterol concentrations This increase in serum lesterol values after the administration of radiol valerate has not been reported earlier

e found that norgestrel both alone and when n together with oestradiol valerate brought ut a significant decrease in the triglyceride con trations and that these values returned to pre tment levels at mid period where oestradiol val te was the only drug administered Investiga ns into the effect of *dl* norgestrel have given what conflicting results (6 7 17) In two dies the *cholesterol* levels decreased (6 7) while triglyceride concentrations fell in two others (6 although this was only significant in one (17) wever it has been shown that 0 075 mg of nor strel caused a more pronounced decrease in glyceride levels than 0 050 mg (6) These findings regard of the triglyceride levels are in agreement th the results obtained in the present study ere 0 500 mg of *dl norgestrel once a day for ten* ys produced a significant fall in triglycerides hneider et al (16) have published the results of an vestigation on somewhat similar lines to those of our study They administered the same sequential drug Cycloprogynon® to 20 post menopausal women with an average age of 52 years They state that there is no significant reduction in serum triglyceride concentrations during treatment cycles as compared to pre treatment and placebo cycles However a closer scrutiny of their reported values shows that the mean values at the end of the therapy cycles are approximately 30% lower than the mean values obtained in mid-cycle at which time the patients had only received oestradiol val erate

Briggs (4) has shown that norgestrel counteracts the influence that many synthetic oestrogens have on serum lipids

In conclusion it may be stated that the norgestrel *component* of the sequential drug Cycloprogy non® is responsible for the decrease in serum triglycerides in climacteric women Further that oestradiol valerate has no significant influence on the triglyceride levels but that it increases the con centration of cholesterol

ACKNOWLEDGEMENT

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COAGULATIVE AND FIBRINOLYTIC STUDIES ON POSTMENOPAUSAL WOMEN TREATED WITH A NEW NON STEROIDAL OESTROGEN

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ract Treatment of postmenopausal women with a steroidal oestrogen (P1496) in a dose of 50 mg a day 3 days before operation for prolapse did not suppress istochemically determined fibrinolytic activator con of the vessel wall Neither was any change found in concentration of P&P-complex (prothrombin factor factor X) factor VIII antithrombin III α_1 anti sin α_2-macroglobulin or the inhibitors of urokinase ced plasminogen activation Nothing suggested a mbogenic effect of this non steroidal oestrogenic pound

nges in the vessel walls have long been thought lay a role in the pathogenesis of thrombosis d (23) showed that the endothelium of certain sels contain activators of the fibrinolytic system son (13) found the release of fibrinolytic vators from the vessel wall during venous oc ion to be deficient and/or the fibrinolytic vator content of the vein walls to be low in 73 % patients with recurrent idiopathic thrombosis same defect in the fibrinolytic system has also n found in women who had thrombosis during use of oral contraceptives and who were free of ptoms and signs of disease when examined (26) he oestrogenic component in combined oral traceptives (12) and oestrogens alone (2 4 14 have been found to increase the frequency thrombotic complications Åstedt (24) found inyloestradiol to lower the fibrinolytic activity of vessel wall but Åstedt & Jeppsson (25) found such decrease following treatment with 17 β tradiol and they concluded that 17 β oestradiol y turn out to be safer than synthetic oestrogens postmenopausal substitution therapy Kullander l Svanberg (15) studied a new non steroidal oestrogenic preparation P 1496 (Sandoz) and found this drug to be effective in the treatment of climacteric symtoms

This paper concerns the fibrinolytic activity in biopsy specimens of superficial veins obtained from postmenopausal women before and after treatment with this non steroidal oestrogen (P 1496) as well as determination of some coagulation factors anti thrombin III and components of the fibrinolytic system

MATERIAL AND METHODS

The clinical material consisted of 10 healthy women aged 45 to 70 (mean 62 4 years) who were to undergo operation for uterine prolapse They were all given P 1496 in a dose of 50 mg a day for three weeks before operation and blood samples for determination of P&P factor VIII anti thrombin III α_1 antitrypsin α macroglobulin and inhibitors of urokinase induced plasminogen activation (urokinase inhibitors) and vein biopsy specimens were obtained before and on the last day of treatment

Evidence of an oestrogenic response in the en dometrium on the last day of treatment which was im mediately followed by the operation (including curettage) was regarded as proof that the patient had taken the drug

Coagulation and fibrinolytic studies

Prothrombin+factor VII+factor X (Owren s P&P test) (19) Normal range in plasma 80–120 %

Factor VII (AHF) (17) Normal range in plasma 60–160 %

Antithrombin III Immunochemical method according to Fagerhol & Abildgaard (6) Normal range in serum 60–140 %

α_1-antitrypsin Immunochemically determined based on the rocket method by Laurell (16) Normal range in serum 80–120 %

α_2-macroglobulin Esterolytic method (9) Normal range in serum 80–120 %

Table I *Fibrinolytic activity of hand veins before and at end of treatment with a non steroidal oestrogen (P 1496)*

The fibrinolytic activity was histochemically determined and is expressed in arbitrary units (see text)

	Range	Median value
Before treatment	5 5–9	7 5
End of treatment	5–10	7 5

Inhibitors of plasminogen activation by urokinase (urokinase inhibitors) Clot method (21) Normal range in serum 60–140%

Fibrinolytic activity in the vein vessel wall The principle of the method (23 20) was as follows Cryostat sections of the specimens collected on glass slides were covered with a plasminogen rich fibrin layer After certain periods of incubation the slides were fixed and stained If plasminogen activators were present they converted plasminogen into plasmin with digestion of the overlaying fibrin layer They varied in size with the activator activity

Vein biopsy specimens were taken—with the consent of the informed patients—from the dorsal side of the hand under local anaesthesia After a longitudinal incision of the skin a 0 5 to 1 0 cm segment of the vein was exposed carefully dissected and excised

The specimens were quickly frozen in rapidly expanding CO_2 to prevent freezing artefacts They were packed hermetically in Parafilm or metallic foil to prevent drying and stored at −60°C

The vein biopsy specimens were cut on an International Harris cryostat in sections (8 μm) which were placed on pre cleaned glass slides Four slides were prepared for each sample The sections on each slide were covered with 0 06 ml of bovine fibrinogen prepared essentially according to Brakman s modification (3) of Astrup & Mullertz (1) double ammonium sulphate precipitation method in a concentration of 1% in phosphate buffer (pH 7 8 ionic strength 0 15) and of 10 μl thrombin (Topostasin 20 NIH units/ml unbuffered saline) The fibrinogen thrombin mixture was spread over an area of 10 cm^2 in order to obtain a fibrin film about 0 07 mm thick To stabilize the fibrin film the slides were left at room temperature (21 to 24 C) in a moist chamber for 30 min One of the slides was immediately fixed in formalin while the remaining three slides were transferred to another moist chamber at 37 C and incubated for 10 20 30 min respectively after which they were fixed in formalin The slides were stained with Giemsa solution and Harris haematoxylin Fibrinolysis was reflected by clear lytic areas in the fibrin film at the site of fibrinolytically active cells Three fairly distinct grades of fibrin digestion were recognized Grade I signified microscopical punctate areas in most of the sections Grade II meant gross lytic areas of irregular outline and sometimes confluent and Grade III meant dissolution of most or all the fibrin in contact with the sections

A Grade I slide was allotted 1 point a Grade II slide 2 points a Grade III slide 3 points The total number of points scored by the set of four slides was taken as a measure of the fibrinolytic activity of the [illegible] The normal range was 6 0 to 10 0 arbitrary units [illegible] value being 7 5

Statistical methods The group were compared [illegible] aid of Students-*t* test The difference in the [illegible] activity of the veins was analysed with Wilcoxon's [illegible] sum test (5)

RESULTS

A high degree of oestrogenic influen[illegible] age was found in the endometrium of all the [illegible] treated The fibrinolytic activity of [illegible] specimens was normal and remained [illegible] during treatment (Table I) Neither were [illegible] changes found in the concentration of [illegible] macroglobulin or urokinase inhibitors The concentration of α_1 antitrypsin was significant[illegible] creased after treatment though still within [illegible] range The values found for the [illegible] factors—P&P complex factor VIII and [illegible] thrombin III—were all normal and no cha[illegible] found after treatment (Table II)

DISCUSSION

Many authors (22 10) have found that the [illegible] of a synthetic oestrogenic preparation such [illegible] mestranol is followed by an increase in fibrinog[illegible] and a slight increase in factor VIII They have [illegible] reported an increase in fibrinogen f[illegible] administration of conjugated equine oestrogen[illegible] large doses But Åstedt & Jeppsson (25) have [illegible] that the natural hormone 17 β-oestradiol [illegible] such effect on the fibrinogen levels

Howie et al (10) found the synthetic oes[illegible]

Table II *Coagulation factors antithrombin III [illegible] components of the fibrinolytic system bef[illegible] the end of the treatment with a n[illegible] oestrogen (P 1496)*

	Before treatment (Mean±S D)	End of treatment (Mean [illegible]
P&P	105 1±14	107 [illegible]
Factor VIII	14[illegible] 4±59 3	14[illegible] [illegible]
Antithrombin III	105±17	96 8 [illegible]
α_1 antitrypsin	96 ± 9 8	111 9 [illegible]
α_2-macroglobulin	114 4±33 5	113 9 [illegible]
Urokinase inhibitors	111 1±23 1	11[illegible]

$p<0\,001$

paration mestranol to lower the antithrombin III ...ity and Fagerhol et al (7) showed that com...d oestrogen progesteron oral contraceptives ...ced the antithrombin III level by about 15% ...dt & Jeppsson (25) however found no ...ificant decrease in antithrombin III during the ... of 17 β oestradiol

... the present study we did not notice any change ...he coagulation factors (P&P-complex factor ... antithrombin III) during treatment with P... which in this respect behaves like a natural ...rogen.

...n increase in the α_2 macroglobulin has been re...ed by Howie et al (10) during the use of ...tranol but no such increase has been found in ...ciation with the use of ethinyloestradiol (24) or ...-oestradiol (25) In the present study no change ... found in α_2 macroglobulin or urokinase in...tors during the treatment with P 1496 However ...ntitrypsin rose slightly from a mean of 96 2% ... 11 9% but was still well below the normal ...r limit (170 %)

... normal content of fibrinolytic activators in the ...el walls and a normal ability to release these ...vators to the blood stream seems to be the most ...ditions for the fibrinolytic defence system ...nst thrombosis As mentioned Åstedt (24) ...d a decrease in the content of fibrinolytic ...vators in menopausal women receiving ...nyloestradiol in a dose of 0 25 mg a day for 10 ... In contrast no such decrease was found by ...dt & Jeppsson (25) in women taking 10 mg of ...-oestradiol a day for 10 days As far as we ...w there are no reports of increased frequency ...hrombosis following treatment with naturally ...rring oestrogens

... the present study a dose of 50 mg P 1496 a day ...paratively lower but given for 21 days did not ...lt in any decrease in the fibrinolytic activators ...he vessel walls (Table I) The investigation thus ...duced no evidence of a thrombogenic effect of P ... a drug found useful in combating climacteric ...ptoms (15)

...s the number of climacteric and post...opausal women given oestrogenic therapy will ...sumably rapidly increase this substitution giv... them relief as stated by Furuhjelm (8) it is of ...st importance that not only the beneficial effect ... also eventual side-effects be carefully investi...ed and charted Besides the risk of tumours ...ndometrial carcinoma mammary carcinoma—that of thrombo embolism seems to be the most important The difficulties in such investigations are however considerable The natural frequency of the diseases mentioned as side effects is obscure and the possibility of fluctuation owing to variation of risk factors—other than the administration of oestrogenic drugs—should warn against too hasty conclusions (pointed out for endometrial carcinoma by Ingelman Sundberg (11))

Coagulative and fibrinolytic studies with available methods to test thrombogenic properties is one way elucidating the thrombogenic risks inherent in oestrogenic drugs Comparison of oestrogens of different kinds natural and synthetic with and without the steroid nucleus to find the most effective and least risky is of both theoretical and clinical interest

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SOME METHODOLOGICAL ASPECTS IN THE PSYCHOSOMATIC GYNAECOLOGY

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tract Psychosomatic medicine—and thus psychoatic gynaecology—is presented as an approach to ised by doctors when meeting the patient At the same e it is a method a technique trying to elucidate the hanisms in the most complicated interplay between psychological somatic and social parts of the ole Some diagnostic methods which can be used in connection are discussed The basic aim of the paper o show the necessity and the possibility for the gyn ologist to use new technique from the psychodiag tic field in his daily practice in order to achieve a ter understanding of his patient s complaints and ds

The psychosomatic approach is equal to good medicine (J Apley)

chosomatic medicine—and thus psychosomatic aecology—cannot be considered as a separate dical speciality It is much more an approach to used by doctors psychologists etc when meet the patient It is based on the conviction that no ient is disturbed exclusively in body or in ind' but it is always *the whole person who is ill* otherwise the whole person is healthy If this be e we can speak neither about psychosomatic eases nor about disorders but only about the chosomatic approach

As Apley (?) pointed out the word psychosoatic is a *heritage* of Cartesian duality with its in tual supermarket unfortunately it strengthens idea that the mind and body are separate

We know both from physiology and psychology at in healthy people all bodily processes and ang s are associated with psychological ones especially emotions—and vice versa This also plies to pathophysiology and psychopathology concerning people when ill pathological changes in the body will be associated with sick emotions and again vice versa This is a highly mechanical view if one speaking about psychosomatic illnesses un derstands only ulcus duodeni asthma bronchiale etc In these diseases most studies have demon strated the connection between emotions and or ganic changes The lack of studies in other diseases does not prove the converse Following the classi cal dialectic way of thinking we must come to the only acceptable conclusion that there is no possi bility of separating bodily from psychological phen omena and that the psychological factors are im portant in all health and in all disease

In this paper we must nevertheless for semantic reasons use the pragmatic sicnetific terminology which sometimes seemingly will contradict our in tentions The only person to solve this personal dilemma is the reader himself through his interpre tations

How much then the psychological factors will influence the particular symptom syndrome dis turbance or disease will depend on the patient s personality structure on his reaction patterns on the special circumstances at the onset of the dis ease on the patient s frustration threshold and on psychophysical maturity and state of development (7) Nevertheless the whole clinical picture will be influenced by the social factors and the whole life situation of the patient

Jores (12) speaks in this connection of human disorders —a group of disorders in which not so much physical injury but rather the patient s prob lems with life and his human failings are expressed

When trying to explain the tentative mechanisms

underlying the psychological influences on bodily changes we can quote a psychosomatic model of Luban Plozza & Poldinger (17) According to this model certain emotions give rise to certain autonomic changes Via the diencephalon and the autonomic nervous system neurotic and unconscious factors exert an effect on the body which may result in functional impairment and damage to the organs

According to the neurophysiologists all stress situations lead to an activation of the hypothalamus which immediately sets protection and defence mechanisms in train along motor visceral and neurohormonal pathways At the same time signals are transmitted to the cerebral cortex so that the emotion is perceived and recognized If the threat to the organism continues the forces maintaining the internal equilibrium must remain active longer This can lead to peripheral functional or even organic disturbances in the system affected Modern anthropology which looks at man in terms of his social and interpersonal relationships emphasizes the conflicts arising out of these relationships and stresses their importance as factors in the causation of psychosomatic disorders Thus for example retirement from an active and highly satisfying occupation can lead to a sudden deterioration in a person s health

In order to understand the complicated multifactorial polydimensional reciprocal interplay when analysing the psychological mechanisms in a clinical picture as demonstrated by a patient it is necessary to use methods that enable an individual psychosomatic diagnosis to be established

As von Zerssen (21) stressed in somatic medicine it has been natural that the clinical investigation of a patient is always complemented by the use of standardized physiological and biochemical examination procedures

In psychiatry this partly became the case with the introduction of the use of psychodiagnostic tests Very occasionally however we can see to it that the diagnostic examination of a patient having a proneness to somatic symptoms is complemented by psychological investigations which could lead to a better understanding of the genesis and the extent of the condition the choice of therapy and often the prognosis of the particular disease

It was the immense contribution of Professor Axel Ingelman Sundberg on whose initiative that the Psychosomatic Research Laboratory at the Department of Obstetrics & Gynaecology was [illegible] in 1973 at Sabbatsberg Hospital in [illegible]

One of the aims and purposes from the [illegible] beginning has been to modify existing [illegible] elaborate some new psychodiagnostic [illegible] which can be used by the gynaecologist [illegible] non psychologically or psychiatrically trained [illegible] and in this way extend the [illegible] strumentarium of the gynaecologist by one [illegible] dimension

A large proportion of patients attending [illegible] particularly gynaecological clinics have [illegible] psychosomatic symtomatology In women the [illegible] productive system and emotions are [illegible] closely related It is much more important to [illegible] *what sort of patient has a disease than what [illegible] disease a patient has* Greater attention to the [illegible] of the person rather than of the disease would [illegible] much to advance our understanding of [illegible] hopefully its relief (1) More needs to be [illegible] about how people feel and in order to [illegible] knowledge we require better techniques A [illegible] important rule in the psychosomatic [illegible] approach is the use of an individual centred [illegible] nique Any psychodiagnostic test should [illegible] following qualititative criteria

1 it should be capable of use in the same [illegible] for all individuals

2 it should be capable of repetition in the [illegible] individual on several occasions in order [illegible] the results and to follow up the development [illegible] individual for instance during the treatment [illegible] der the varying influences of the individual's [illegible] psychic or physical processes (19)

3 some tests should allow a quantitative [illegible] of the results and use of statistical methods

4 the test when used in clinical praxis [illegible] easy to administer and not too time-consuming

5 the evaluation of the test should not be [illegible] complicated For example when used [illegible] gynaecologic unit in order to assess [illegible] disturbances the administration and [illegible] must be practicable even for non [illegible] and non psychiatrically trained staff

6 the test must give a reliable [illegible] patient s main problems and conflicts and [illegible] also make it possible to detect pathological [illegible]

In the psychosomatic laboratory of [illegible] Gynaecologic Department Sabbatsberg [illegible] we divided the psychodiagnostic [illegible] seven groups

Techniques and inventories focused case history

Here not only the life events previously experienced but also patients attitudes and evaluations and their changes are registered

When looking through these types of scales one gets an immediate impression of the patient s basic needs wishes disappointments and even some personality traits which can all give a very important background to the patient s present problems

The following are a few examples of the evaluation scales

Mark with × your present attitude to	Satisfaction	Disappointment
sexual life	☐	☐
own education	☐	☐
own occupation	☐	☐
choice of partner	☐	☐
own children	☐	☐
own family life	☐	☐
own friends	☐	☐
own economic situation	☐	☐
realization of previous dreams and expectation	☐	☐

my present life situation I feel (mark with ×)	Agree	Disagree
bitterness	☐	☐
joy	☐	☐
general satisfaction with life	☐	☐
disappointment	☐	☐
happiness	☐	☐
resignation	☐	☐
harmony	☐	☐
love fulfillment	☐	☐

Mark with × in the table below to what degree the following things are important

	Very important	Important	Less important	Unimportant
to succeed	☐	☐	☐	☐
to eat	☐	☐	☐	☐
to be accepted	☐	☐	☐	☐
to be perfect	☐	☐	☐	☐
to be loved	☐	☐	☐	☐
to have sexual desire	☐	☐	☐	☐
to be comfortable	☐	☐	☐	☐
to be secure	☐	☐	☐	☐
to love	☐	☐	☐	☐
to be happy	☐	☐	☐	☐
to make love	☐	☐	☐	☐
to win	☐	☐	☐	☐
to have many friends	☐	☐	☐	☐
to have children	☐	☐	☐	☐
to be intelligent	☐	☐	☐	☐
to be beautiful	☐	☐	☐	☐

II *Personality tests*

The large group of personality tests and questionnaires many of which can be filled in by the patients themselves and evaluated by doctors in an often not too-complicated way offers in many cases a fairly good picture of the patients basic personality traits In this way one can understand much better the patients complaints their meaning and symbolic values and not infrequently also predict their further development

As an example from this group we can mention the Eysenck Personality Inventory (5) which is used for measuring neuroticism and extraversion/introversion personality dimensions considered by Eysenck as basic traits In several of our research projects (8 9 10) we have demonstrated the valuable use of this test both in the diagnosis and in the follow up of the treatment

III *The projective techniques*

This group of tests represents a possibility for the patients to express unconscious conflicts fears wishes etc The best known and the most perfect test in this group is the Rorschach test (18)

A very simple but widely informative projective procedure has been elaborated (10) The test consists of 90 complete sentences with varying degrees of emotional relevancy for the individual patient Example a 24 year-old girl with secondary amenorrhea associates as follows

I feel	ugly
I long to	look as I did 3 years ago
I am most afraid of	illness and death
I dream about	freedom
A mother	I feel sorry for her
Being a woman	frightens me
I wish	I were a child again
My thoughts	frighten me
It hurts me	to be the way I am
I dislike	femininity
My mother	I can never be free from
Being a mother	is not my dream
I am not afraid of	aggression
A man	frightens me

IV *Methods for measuring depression*

In accordance with Kielholtz (14 15) Kielholtz et al (16) and Battegay (3) we are also of the opinion that depression is a syndrome with many different etiological causes and represents a reaction of the

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UTERINE ACTIVITY IN DIABETES INSIPIDUS

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ract In two nonpregnant women with cranial diabe nsipidus myometrial activity under different hormon nditions was studied by intrauterine pressure record Recordings were performed when the women were r the influence of their regular treatment with des nocys D-arg[8] vasopressin (DDAVP) and when they fully developed symptoms of their disease Uterine vity was similar to that found in normal women under same hormonal conditions and generally did not ge when symptoms of lack of vasopressin appeared DDAVP (15–20 μg) given intranasally and lysin pressin (0 2 IU) given intravenously stimulated uter activity particularly in late secretory menstrual phase s suggested that endogenous vasopressin is of minor ortance for the induction of spontaneous uterine ac y in nonpregnant women

the two posterior pituitary hormones oxytocin s powerful myometrial stimulant in pregnancy ticularly at term and is believed to play a siological role in the induction of labour It is vever almost ineffective in the nonpregnant state Vasopressin has little effect on the pregnant rus at term (8) but it is a very potent stimulator the nonpregnant myometrium (5 7 10) During menstrual cycle there are also variations in ometrial sensitivity to vasopressin (2 5 7 10) e effect is most pronounced at the onset of men uation and minimal at midcycle These varia ns in sensitivity of the myometrium correspond the variations occurring in spontaneous myo trial activity throughout the menstrual cycle (1) It is not known however whether vasopressin ys a physiological role in the induction of spontaneous uterine activity in nonpregnant wom en An opportunity to study this problem is of fered in women with cranial diabetes insipidus in whom there is an insufficient endogenous produc tion of vasopressin In the present study two wom en with this disease were investigated as to their spontaneous uterine activity throughout the men strual cycle

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MATERIAL AND METHODS

Subjects

Patient U C born 1944 had been previously healthy when her diabetes insipidus suddenly developed in 1963 There was no family history of the disease Without medi cation the patient produced about 18–20 l of urine per day Thorough investigations at the University Hospital Lund Sweden revealed no signs of other disorders and it was concluded that she suffered from the idiopathic type of diabetes insipidus She was given replacement therapy with desaminocys[1] D-arg[8] vasopressin (DDAVP) (Mini rin® Ferring Sweden) 20 μg taken intranasally 2–3 times per day As a result of this treatment her daily urine production was reduced to normal (volumes 0 9–1 7 l/day urine osmolality 450–780 mOsm/kg H_2O) and she could lead a normal life The patient had been pregnant twice since the start of the disease in 1968 and 1971 and she delivered spontaneously 3 and 5 days after expected time respectively without any complications In the puer perium she experienced slightly painful uterine con tractions after the second delivery but not after the first She nursed her second child for a period of 3 months after the delivery Both her infants are at present healthy and developing normally

During the present investigations she had regular men strual cycles of 28–30 days with menstruation of 4 to 5 days duration Her basal body temperature chart showed a biphasic pattern Progesterone and oestradiol estima tions on plasma samples taken the day of the recordings were within normal limits (13) indicating that she had ovulatory menstrual cycles Gynecological examination

cle (Fig 1) and more pronounced at the end of the secretory phase (Fig 2) or during combined oestrogen and gestagen therapy (Fig 3)

DDAVP had a slight stimulatory effect on uterine activity appearing within 5 min after intranasal administration (Figs 1 and 2) The stimulatory effect of LVP given intravenously was more pronounced especially in terms of frequency of contractions and of uterine tone (Figs 2 and 3) The local endometrial blood flow decreased after administration of vasopressin (Fig 3) in agreement with what has been found in normal women (2)

After administration of DDAVP or LVP the specific gravity and volume of urine produced were both within normal limits

DISCUSSION

The possible physiological role of vasopressin in the induction of uterine activity in nonpregnant women has previously been studied by infusion of iso-oncotic solutions in order to inhibit the endogenous secretion of vasopressin (9) In those experiments a complete inhibition of myometrial activity during menstruation was obtained in the majority of the investigated women It was suggested therefore that vasopressin may be a physiological stimulus for uterine contractions during menstruation A more direct way of analyzing the effects of a lack of vasopressin is to study uterine activity in women with diabetes insipidus This also excludes other possible effects due to the infusion of large amounts of fluid

The women in the present study had previously been shown to have an insufficient vasopressin production as judged from the results of water deprivation tests and inability to increase their urine osmolality in response to hypertonic saline infusion (Carter Robbins test) Furthermore administration of vasopressin could completely relieve their symptoms

The woman with idiopathic diabetes insipidus receiving regular treatment with DDAVP seemed to have a quite normal reproductive function She had been delivered of two children spontaneously since the start of the disease and had nursed her second child She had also spontaneous ovulatory menstrual cycles The other woman had an insufficient endogenous production of ovarian hormones and in addition her substitution therapy seemed to be insufficient as menstruation did not start until 5 days after stopping the cyclical treatment Furthermore her uterine activity the day before the [illegible] of the withdrawal bleeding was minimal

The uterine activity in the two women during the time they still were receiving regular treatment [illegible] DDAVP did not seem to differ from that [illegible] women in the same ovarian hormonal [illegible] The symptoms of diabetes insipidus had developed [illegible] dicating a lack of vasopressin this generally did [illegible] influence the recorded spontaneous uterine activity The only exception to this was one recording [illegible] the patient with idiopathic diabetes in[illegible] investigated during early secretory menstrual phase when the uterine activity decreased

In conclusion the results of the present [illegible] suggest that endogenous vasopressin is of [illegible] importance for the induction of spontaneous uterine activity in nonpregnant women Other [illegible] stimulants such as E and F prostaglandins are probably factors of major importance [illegible] at least around the onset of menstruation

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FUNCTIONAL ROLE OF AN ADRENERGIC SPHINCTER IN THE FEMALE URETHRA OF THE GUINEA PIG

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tract By means of a microtransducer catheter the thral *pressure* profile was recorded in female guinea s The maximum urethral *pressure averaged 24 mmHg* nge 18–27 mmHg) and was found 4 to 7 mm from the a o-urethral junction Fluorescence microscopy of the thra showed an irregular distribution of fluorescent ve terminals in the most proximal part of the organ In istal direction there was a continuous increase in the mber of adrenergic nerves with a maximum 4 to 6 mm m the internal meatus corresponding to the maximum raurethral pressure point In this region a dense plexus nerves supplied thick muscle coats of smooth muscle n g an outer circular and an inner longitudinal orienta n The findings suggest that a specific region of the nale guinea pig urethra may serve as an internal hincter

vidence has been presented suggesting the ex tence of a functional sphincter in the proximal part the urethra both in different animal species and man (8 11 13 15 18) A great number of pres re profile measurements in human female urethra ve clearly demonstrated an intra luminal pressure ak at a distance of *11–12* mm from the inner eatus of the *urethra* (1) This finding confirms the istence of a functional urethral sphincter No orphological arrangements convincingly showing sphincter *mechanism* have however so far been und (4 5 17)

Several studies have stressed the importance of he adrenergic nervous system for the function of h internal" sphincter Histological investigations f the adrenergic innervation of the urethra of cat og and rat have shown a rich occurrence of drenergic nerve terminals (2 14 16) especially abundant in the muscle of the proximal urethra (14) The role of the adrenergic innervation for the sphincter function has however not been settled

The aim of the present investigation was to find out whether a relationship exists between the ad renergic innervation pattern and the intraurethral *pressure profile*

MATERIAL AND METHODS

The study was performed on 11 female guinea pigs weigh *ing 3_0–480 g*

Pressure recordings

Technique The intravescial and intraurethral pressures were recorded by means of a previously described techni que for simultaneous u ethro-cystometry and urethral pressure profile measurement (1) The intraluminal pres sures are recorded by means of a micro-transduced en clo ed in a semiflexibl dacron catheter The active pres sure sensor area of the micro-transducer is only 0 75 mm and the outer diameter of the catheter is 1 6 mm The frequency response of the recording system is more than 1000 Hz (19) After amplification the pressure signals were recorded by an ink jet recorder (Siemens-El ma No 81)

Experimental procedure Af er anesthesia with pentobarbital th recording catheter was introduced transurethrally so far that the micro-transducer at the tip of the catheter was placed in the bladder The intravesical pressure was recorded for about one minute The catheter was then connected to a specially designed withdrawal instrument (1) Using this instrument the catheter includ ing the micro-transducer was pulled backwards at a con stant rate of 3 6 mm/sec By this manoeuvre the intralum inal pressure was continuously recorded throughout the entire length of the urethra from the inner to the outer meatus = the urethral pr ssure profile (Fig 1)

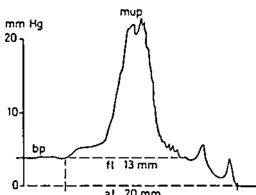


Fig 1 Representative urethral pressure profile from one of the guinea pigs *bp* Bladder pressure *mup* maximal urethral pressure *fl* functional length of the urethra *al* absolute length of the urethra

Fluorescence histochemistry

After completing the pressure recordings in the intact animal the abdomen was opened by a lower midline incision and the symphysis was transected to expose the urethra The recording device was again inserted and could easily be recognized through the thin translucent wall By moving it through the lumen it was possible to confirm the exact anatomical point corresponding to the pressure maximum A 5 mm long portion of the urethra including this point and two additonal adjacent pieces of the same length distally and proximally were dissected out and immediately frozen in a propane propylene mixture to the temperature of liquid nitrogen

In addition to the pieces obtained from these 7 animals the entire urethra was removed from a further 4 untreated *animals and frozen in 3 pieces of equal length*

After freeze drying the preparations were exposed to gaseous formaldehyde at +80°C for 1 hour to visualize the adrenergic transmitter noradrenaline (9) Following paraffin embedding *in vacuo* 6 μm thick serial transverse sections were prepared and mounted in Entellan (Merck) fluorescence microscopy For further technical details Bjorklund et al (3)

RESULTS

Fluorescence histochemistry

The smooth musculature in the entire length of the urethra was supplied by adrenergic nerve terminals characterized by a beaded (varicosed) appearance and emitting an intense green fluorescence under the optical conditions used Serial sectioning of the organ revealed a clear regional variation in the amount of muscular nerve fibres the most proximal part was characterized by an irregular distribution of scattered fluorescent terminals together with axons enclosing several small blood vessels (Fig 2) In a distal direction there was a continuous increase in the number of adrenergic nerves until was reached approximately 4-6 mm der In this region (Fig 2) a dense p supplied thick smooth muscle coat an outer circular and inner longi This was followed by a fairly rapid nerve density in (Fig 2) Here again the fluorescent more irregular fashion reflecting arrangement of the smooth muscle fibres tal part of the urethra contained n shaped enterochromaffin like cells in the epithelium Occasionally it was seen that the adrenergic axon terminals were underneath this epithelium

Pressure recordings

In all animals the intravesical pressure was stable and varied between 2 and 5 mmHg (mean mmHg) The intraurethral pressure varied in different parts of the organ The highest intraurethral pressure was recorded in midurethra 4 to (mean 5 mm) from the inner meatus where the maximal pressure amplitude was found to average mmHg (range 18 to 27 mmHg) The functional length of the urethra i e the region where the intraurethral pressure exceeds the intravesical pressure varied between 12 mm and 16 mm (mean mm) The absolute length of the urethra i e the region where the intraurethral pressure exceeds the atmospheric pressure was difficult to evaluate in some cases but varied between 16 mm and 23 mm (mean 18 mm)

Fluorescence microscopy of that part of the urethra in which a pressure maximum was recorded showed an exact correspondence with the most pronounced supply of adrenergic nerves in the smooth muscular wall (Fig 2)

DISCUSSION

The sphincter function of the lower urinary tract is still a matter of discussion Thus the internal sphincter is not established and it is not settled whether the bladder neck or any part of the urethra can serve as the internal sphincter Lapides (12) concluded on the basis of experiments performed mainly on dogs that "the internal vesical sphincter is a tubular muscular segment synonymous with the posterior urethra in the male or the entire urethra in the female" Gleason et al

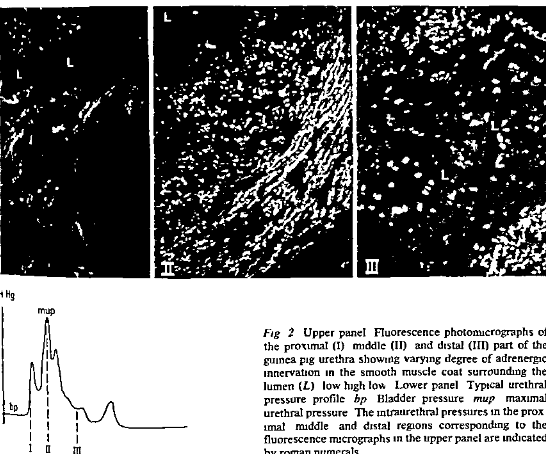


Fig 2 Upper panel Fluorescence photomicrographs of the proximal (I) middle (II) and distal (III) part of the guinea pig urethra showing varying degree of adrenergic innervation in the smooth muscle coat surrounding the lumen (*L*) low high low Lower panel Typical urethral pressure profile *bp* Bladder pressure *mup* maximal urethral pressure The intraurethral pressures in the proximal middle and distal regions corresponding to the fluorescence micrographs in the upper panel are indicated by roman numerals

) studying the urethral pressure profile in man gested that the extreme sensitivity of con ence to urethral pressure must localize the conti nce mechanism to the urethra They found a cific zone of the urethra to be critical in mainte nce of continence and that the bladder neck did t appear to be a critical part of the continence chanism

Studies on the distribution of adrenoceptors and olinoceptors in the isolated human urethra and the effects of drugs stimulating these receptors gested that the response to adrenoceptor imulating agents was similar throughout the or n including the urethrovesical junction (6) Thus ere was a predominance of contraction mediating adrenoceptors relaxation mediating β adreno- ptors could be demonstrated The response to olinoceptor stimulation on the other hand emed to be insignificant In all parts of the ethra there was a scanty but rather uniform sup- ly of adrenergic nerves (7) These findings suggested that the sympathetically innervated smooth muscle is capable of contributing to the intraluminal pressure in all parts of the urethra and gave no evidence for a sphincter function in any particular part of the organ The present result obtained in female guinea pigs showed that the most proximal part of the urethra had an irregular distribution of fluorescent terminals but that there was a distinct increase in the number of adrenergic nerves more distally reaching a maximum approximately 5 mm from the bladder In this region a dense plexus of nerves supplied thick smooth muscle coats that had an outer circular and an inner longitudinal orientation These findings suggested that this part of the urethra could serve as the internal sphincter and this assumption was supported by the measurements of the urethral pressure profile There was an exact correspondence between the point where the maximum intraurethral pressure was recorded and the most pronounced supply of adrenergic nerves

The information is scarce concerning the

ences in the anatomical structure of the urethra that may exist between different experimental animals Little is also known about the distribution of adrenoceptors and cholinoceptors and the sensitivity to drugs stimulating these receptors This should be borne in mind when studies on the urethral function in animals are compared and especially when comparing data from animal studies with those obtained in man

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PUBOCOCCYGEAL REPAIR AD MODUM INGELMAN SUNDBERG

A Retrospective Investigation with 10–20 Years Time of Observation

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tract Fifty-one women operated on for stress inconti
ce with pubococcygeal repair ad modum Ingelman
dberg between 1955 and 1965 were investigated uro-
ecologically The time of observation was accordingly
ast 10 years in every case An evaluation was made of
operation method the distribution of recurrences dur
the postoperative period and possible side effects
it women had symptoms of at least degree I stress
ntinence and thirteen showed signs of incontinence at
l examination Only four had both symptoms and signs
continence The cure rate from a symptomatic point
iew was 84% and from the technical aspect 75% Most
e severe recurrences occurred in the first postopera
year Thereafter the recurrences were evenly distri
d The only side effect in the long run was a tendency
ectocele

ss incontinence is a dysfunction rather than an
ss and occurs only in homo It involves in
ntary urinary leakage at a sudden rise of the
a-abdominal pressure It can be classified as
ws (15)

gree 1 Urinary leakage only at coughing or
neezing

gree 2 Leakage also at changing position mov
ng fast or walking up stairs

gree 3 Leakage even at minimal straining in the
tanding position

ring the last decades the genesis of stress incon
nce has been thoroughly investigated and
died Interest has focused on the anatomical and
siological changes in the bladder neck and the
ximal urethra during voiding and on pressure
ations in the bladder and the urethra at a sudden abdominal increase of pressure Several hypotheses concerning the genesis of stress incontinence have been presented and given rise to a growing variety of operation methods

At the beginning of the 1960s Enhorning (7) using simultaneous urethrocystometry showed that a sudden rise of the intra abdominal pressure normally is transmitted not only to the bladder but also to the proximal third of the urethra which is to be considered an intra abdominal organ In cases of stress incontinence the bladder neck and the proximal urethra are lowered dorso-caudally so that a sudden pressure rise e g at coughing only reaches the bladder and not the urethra The urethra cannot produce a sufficient pressure when in a lowered position in spite of the fact that the intraurethral pressure at rest is always higher than the corresponding bladder pressure Thus according to Enhorning stress incontinence appears for hydrodynamic reasons It is still unclear whether a lowered bladder neck alone explains the leakage Insufficiency of an internal and/or external sphincter (18 19 22) funnelling of the proximal urethra (1 12 21 27 28) an abnormally short urethra (20) and a more or less pathological posterior urethrovesical angle (9 10 16 17 26) have also been put forward as plausible explanations As basic causes of these changes of the uro-genital anatomy a general insufficiency of the connective tissue menopause pregnancy and vaginal deliveries have been reported (3 6 8) However no direct correlation exists between parity and the occurrence or severity of stress incontinence and the dysfunction occurs even in nulliparous women

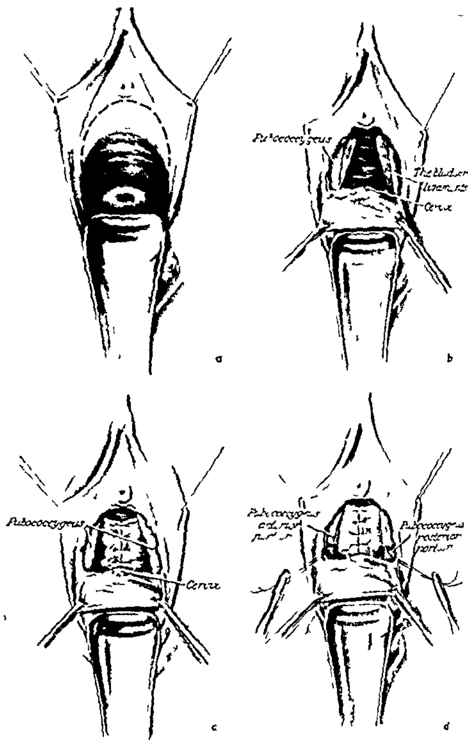
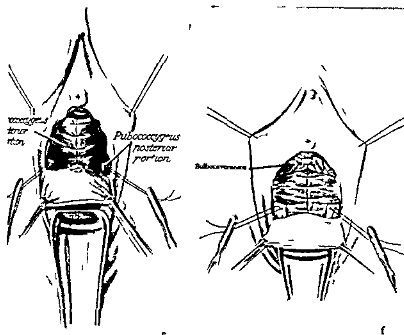


Fig 1 a–d For explanation see text By permission of Axel Ingelman Sundberg

Since a lowered position of the bladder neck seems to be the main reason for stress incontinence it is essential to choose an operation method that elevates this region e g urethropexia ad modum Marshall Marchetti Krantz Kelly s operation va ious types of sling operations The p bococcyg repair operation ad modum Ingelm n Sundberg is from a theoretical and physiological poin



1 e-f For explanation see text By permission of Axel Ingelman Sundberg

suitable for severe degrees of stress incontinence It makes use of the patient s own muscles (pubococcygei the medial portions of the levator muscles) which are sutured under the bladder neck as a hammock with contractile ability At holding urine this hammock is supposed to contract and elevate the bladder neck and the proximal urethra in an antero-cranial direction

Previous retrospective investigations performed on incontinent patients after other operation methods have mostly been made at an observation time of 5 years or less Since recurrences are sometimes seen later it is of interest to study a group of patients who have all been observed for 10 years or more after the surgical treatment The patients now investigated had all been operated on according to the standard method for pubococcygeal repair ad modum Ingelman Sundberg between 1955–1965 Thus the observation time is 10–20 years The aim of the investigation was to evaluate the effect of this operation method and the distribution of the recurrences during the postoperative period The main indication for operation was stress incontinence but cases of incontinence caused by scar tissue were also represented Some of these patients had already been operated on several times because of stress incontinence The results are not to be compared with those of other investigations where cases of pure stress incontinence have been selected and operated on for the first time In 1952 Ingelman Sundberg (14) made a follow up of 82 patients operated on with pubococcygeal repair on the indication stress incontinence The observation time was 2–5 years Seventy seven patients were cured and 5 improved This good result was achieved even though 4 patients had a vaginal delivery during the observation period The cure rate in this follow up was 94% For some patients the observation time was short but still the method seemed to be suitable for treatment of stress incontinence In 1964 Christensen & Østergaard (5) made a follow up on 40 stress incontinent patients operated on with pubococcygeal repair and with an observation time of 0 5–9 5 years and got equally good results The same year Ochshorn (24) reported similar results

MATERIAL AND METHOD

Included were 51 patients who underwent the pubococcygeal repair operation between 1955–1965 Excluded

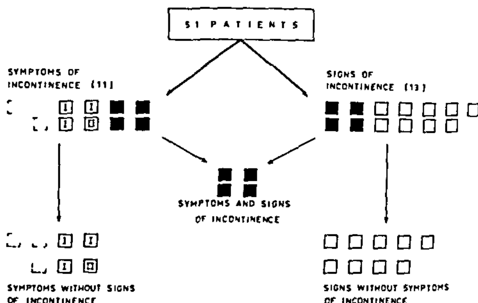


Fig 2 Recurrences 10–20 years after pubococcygeal repair The Roman numerals inside the squares signify the degree of incontinence The dotted squares mean 1st degree of incontinence periodically only

were 88 patients mostly living in distant parts of the country who could not be traced or had no opportunity to come for an examination All patients had been thoroughly examined uro-gynecologically before the operation This meant neurological control of the S1–S4 dermatomes sphincterometry (ad modum Leander) urethrocystoscopy cystometry (Lewis) and Bonney s test

The mean age at the operation was 66 years (r=86–47) and the mean parity 2 (r=4–0) The mean duration of stress incontinence of degree 1 before operation was 9 years degree 2 2 5 years degree 3 0 5 years

Five patients hade been operated on previously because of incontinence Another 5 patients had been operated on with the Manchester operation

A small group of 14 patients operated on during the same time with plasty of the bladder floor i e suture only of the bladder ligaments (pelvic fascia) was also examined to investigate if there were any differences regarding the frequency of recurrences The mean age and parity for this group were approximately the same as in the group operated on with the pubococcygeal repair

Operative technique ad modum Ingelman Sundberg (Fig 1 a–f)

An arcuate incision is made below the external urethral meatus (Fig 1*a*) The anterior vaginal wall is dissected from the urethra and the bladder floor up to the cervix (Fig 1*b*) The bladder ligaments are dissected and sutured in the midline from the proximal urethra to the cervix to which the innermost suture is fixed (Fig 1*c*) Continence is checked with 300 ml bladder volume at repeated coughs The pubococcygeal muscles are dissected and totally divided just below the middle (Fig 1*d*) The anterior portions of the pubococcygeal muscles are sutured under the bladder neck and the proximal part of the urethra so that a muscle sling is formed (Fig 1*e*) The bulbocavernous muscles are sutured in the midline without division as a support for the distal part of the urethra (Fig 1*f*) The posterior portions of the pubococcygeal muscles are sutured bilaterally to the ischiocavernous muscles The anterior vaginal wall is sutured at the introitus a suprapubic catheter is applied as well as a vaginal tamponade

Experimental performance

The patients were examined in the lithotomy position with a gynecological status The degrees of cystocele urethrocele and rectocele were noticed as well as the degree of downward rotation of the anterior vaginal wall at coughing The presence of urinary leakage at a bladder volume of 300 ml at repeated coughs was checked. In cases of leakage Bonney s test was performed Preferably leakage should have been controlled also in a standing position but this was impossible in some cases because of the fragility and high age of the patients Residual urinary volume was estimated The history was thoroughly penetrated concerning the time for and degree of recurrence Besides the case reports of the patients were checked regarding previous operations degree and duration of the incontinence before the pubococcygeal repair

RESULTS AND DISCUSSION

Eleven out of 51 patients reported *symptoms* of incontinence during the postoperative period (Fig 2) Only in 4 cases could urinary leakage be confirmed at examination One of the remaining seven patients had got symptoms similar to those before the operation and the others had symptoms of a

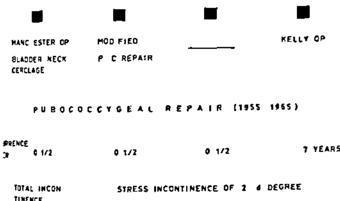


Fig 3

nor degree Three of them had symptoms only sporadically at infections or anxiety and as no signs of leakage were seen it seemed doubtful whether they were recurrences at all They were therefore not counted when the cure rate was calculated

Signs of urinary leakage were confirmed in no less than 13 patients Nine of these had no symptoms at all

Four patients had both *symptoms and signs* of incontinence (Fig 3) The first was previously operated on with a Manchester operation and cerclage of the bladder neck The pubococcygeal repair was done partly on the indication scar incontinence and became a primary failure The patient has had a urethral negative total incontinence since then

The second patient had previously been operated for vaginal endometriosis and for incontinence with an incomplete pubococcygeal repair where the pubococcygeal muscles had only been half cut so in this patient the complete pubococcygeal repair operation was performed partly on the indication scar incontinence and became a primary failure

The third patient had not been operated on before but got a recurrence of the same degree as before operation After another sling operation and urethral kinking she is now improved but not cured

The fourth patient had been operated on ad modum Kelly before the pubococcygeal repair She got a recurrence after 7 years and had a stress incontinence of second degree at the examination

A weak correlation was observed between patients with incontinence symptoms and those with signs at the investigation This could be partly explained by the fact that minimal urinary leakage is difficult to confirm at examination in the supine position One could suppose that the patients shown to leak had arranged their daily lives so that no leakage inducing strain was allowed to occur and therefore they claimed to have no symptoms Perhaps they eliminated the risk of leakage by voiding often and avoiding coughing straining moving fast lifting and so on

To study if there was also a psychic component influencing the presence or absence of symptoms a personality test was performed (29) At this psychodiagnostic investigation the degrees of depression and neuroticism (the disposition to react in a neurotic way) were estimated in 33 of the 51 patients It was thereby concluded that the patients with symptoms of urinary stress incontinence irrespective of signs had a higher degree of both depression and neuroticism than the others

The patients with symptoms and signs got their recurrences almost immediately In fact two of them were primary failures without even temporary improvement Possibly this was caused by a rupture of the muscle sling If this was the case it would perhaps be wise to reoperate such patients as soon as possible before scarring worsens the outlook The other symptomatic recurrences were evenly distributed during the postoperative period (Table I)

Regarding symptoms the cure rate was 84% If the 2 patients with incontinence due to scarring are excluded the cure rate for the selected pure stress incontinent patients was 88%

From a technical point of view the patients with

Table 1 *Time of recurrence*

Years after op	No of recurrences
0– 3	6
4– 5	1
6–10	2
10–20	2

signs are recurrences although most of them did not complain of incontinence symptoms On this premise the cure rate was 75 %

In the group of patients with *signs* of urinary incontinence 7 out of 13 had an abnormal lowering *of the vaginal wall at straining The corresponding* number for those with *only symptoms* was 1 out of 7 and for the *cured* patients 2 out of 31 Thus a clear correlation existed between signs of urinary leakage and lowering of the vaginal wall As the lowered position of the bladder neck and the proximal part of the urethra has long been considered to be the main cause of stress incontinence (2 4 7 11 23 25) it seems doubtful if the patients with only symptoms and without any lowering of the vaginal wall should be regarded as recurrences Also considering the results of the psychodiagnostic investigation these patients are possibly not to be affirmed stress incontinence recurrences If the patients with both an abnormal lowering of the vaginal wall and signs or severe symptoms of incontinence are counted the cure rate was 85 %

The frequency of rectocele after the pubococcygeal repair was high The reason for this could be that the medial portion of the m levator ani had en cut A contributing factor could be that the terior vaginal wall is very firm postoperatively and that because of this the posterior wall gives away at straining In 22 of the 51 patients the pubococcygeal repair was combined with a posterior colporaphy because of rectocele Eleven of these 22 patients got recurrences of their rectocele Another 17 in whom no posterior colporaphy had been done got rectocele during the observation time As stress incontinence is probably at least partly a kind of insufficiency of the connective tissue one could presume the frequency of rectocele to be higher in these women than normally Because the incidence of rectocele was almost the same independently of the patients being operated on for rectocele or not it seems logical to combine pubococcygeal repair with posterior colporaphy only in cases of troublesome rectocele

No certain conclusions could be drawn concerning the possible correlation between parity and stress incontinence The mean parity and the distribution of nulliparous women were the same in the group with symptoms of incontinence and the group with signs

The small group of patients operated on with only bladder ligament suture had a symptomatic cure rate of 43 % and a technical cure rate of 64 % When the cure rate was based on an abnormal lowering of the vaginal wall combined with signs or symptoms of incontinence it was 77 % The recurrences were evenly distributed ranging from 1 to 18 years with a mean of 7 years *It is therefore possible that the* muscle sling is necessary to obtain a good and lasting result

CONCLUSION

This investigation aimed at studying what happens in the long run (10–20 years) after pubococcygeal repair ad modum Ingelman Sundberg There are two ways of estimating the cure rate from the patient s point of view or from a technical aspect The cure rates were 84 % and 75 % respectively Most of the recurrences occurred during the first postoperative year These included the most serious cases in which since then several re operations have been performed without success The other recurrences were evenly distributed during the long observation time The only side effect of the operation in the long run seemed to be a tendency to rectocele It is useless to combine the pubococcygeal repair with a posterior colporaphy unless trouble from the rectum is present Comparison with a small group of patients operated on with only plasty of the bladder ligaments showed that in the long run the muscle sling was an advantage for the cure rate Considering these results and the long observation time the *pubococcygeal repair* method seemed to be most suitable for patients with serious urinary stress incontinence and affords a good chance of curing the patients for life

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INGELMAN SUNDBERG OPERATION FOR URINARY INCONTINENCE

Our Experience

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ract The authors analyse the indications for the lman Sundberg operation considering pelvic ana r previous surgery and the age of the patient The ation is described with pre and postoperative man nent Associated operations such as perineorraphy the amputation of the uterine cervix are mentioned lly a study is made of the experience of the ecologic Clinic of the Catholic Faculty of Medicine ating the postoperative problems that have arisen the results obtained in the cure of urinary incon nce The surgical treatment of urinary incontinence to lesions of the pelvic floor presents several dif lties with a high incidence of recurrence of symptoms

earch of a solution for the problem many surgi techniques have been proposed some involving upra pubic approach such as the Marshall–rchetti–Kranz and Burch techniques others the inal route in which the Kelly operation de bed in 1911 is the original technique and the s of others with lifting of the base of the blad and lengthening of the urethra

The Ingelman Sundberg operation involves the of pubo-coccygeus along with the principles cribed by Kelly The original incision curves nsversely across the vagina with the concavity ing posteriorly and inferiorly and the pubo-cygeus muscles are completely divided in order construct a muscular belt under the base of the adder

The use of the pubo-coccygeus had previously en strongly recommended for reducing the mber of recurrences Suture of the pubo-ccygeus muscles together in the mid line was de ribed by Martius by Kennedy and by other au ors However there is a tendency to separation hen the muscles contract Previously partial divi on of the pubo-coccygeus had been proposed by several surgeons such as Squier Franz and Taussig The problem is that in time the muscle fibres lose their contractility and become atrophied

Ingelman Sundberg taking into account the fact that the pubo-coccygeus receives blood vessels and nerves from both sides perfected the complete division of the muscle and the shaping of a belt passing under the base of the bladder by suturing the two parts together This belt is under voluntary control and therefore aids the control of micturition At the Gynecologic Clinic of the Catholic Faculty of Medicine of Porto Alegre (Chairman Prof J Gomes da Silveira) the Ingelman Sundberg operation was introduced for the surgical treatment of urinary incontinence when associated with urethrocele or small cystocele and when the patient has already been subjected to a hysterectomy

We consider as contra indications for this technique the presence of large cystoceles where the incision is unsuitable for colporrhaphy uterine retroversion and a history of previous vaginal surgery for uterine prolapse

MATERIAL AND RESULTS
(25 operations)

Indications

Small cystocele with urethrocele 22 cases (88%)
Large cystocele with urethrocele 3 cases (12%)
Incontinence of urine 25 cases (100%)
Previous hysterectomy 2 cases (8%)

Age

<20 years 1 case
20–30 years 4 cases
30–40 years 12 cases
40–50 years 7 cases
50–60 years 1 case

Associated operations

Amputation of the uterine cervix 5 cases (20%)
Perineorraphy 21 cases (88%)

Complications

Urinary infection 5 cases (20%)
Urinary retention 2 cases (8%)
Hemorrhage 1 case (4%)

Our results during a maximum period of three years

Cure 23 cases (92%)
Recurrence 2 cases (8%)

CONCLUSION

In our experience from the technical point of view the surgery presents the following advantages (1) Utilization of the voluntary mechanism for urinary control (2) The incision favors approach to the urethra avoiding large vaginal incisions in cases involving urethrocele without cystocele (3) It does not use the cervix as point of reference and traction, which makes it suitable in cases of patients who have undergone hysterectomy

The post-operative period requires special care in the drainage of the bladder which is achieved by a supra pubic drain which remains open for the first 24 hours After this period the drain is closed and spontaneous micturition encouraged Our average period during which the drain is kept in place has been three days

The hospitalization period has varied from five to nine days We have emphasized post-operative exercises to contract and relax the pubo-coccygeal muscles

Submitted for Festschrift

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INFRAVESICAL NERVE RESECTION FOR DETRUSOR DYSSYNERGIA

The Ingelman Sundberg Operation

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1959 a paper was published in Acta Obstet Gynecol nd (38 487 1959) by Axel Ingelman Sundberg (1) en d Partial Denervation of the Bladder—a new opera for the treatment of Urge Incontinence and similar ditions in women" The basis for the operation was ted in the initial sentence The function of an auto-nous neurogenic bladder is usually superior to that of a rogenic bladder where higher centers are still partially nction His operation consisted of transection of the ganglionic pelvic nerves near the inferior surface of the dder and involved division of both the sympathetic and parasympathetic nerves

a preliminary test to the operation Ingelman ndberg employed continuously recorded ret grade water cystometry and recorded the first sire to void bladder capacity sphincter pressure d residual urine volume Following the initial stometric study he injected 0 25% xylocaine th epinephrine 0 005% into one super lateral vag al fornix 1 cm lateral to the cervix at a depth of 3 n. After waiting 5 minutes the cystometric study as repeated If all inhibited bladder contractions opped by unilateral injection the investigation was opped However if uninhibited contraction con nued or if bladder capacity was still too small ylocaine injection was made into the opposite for ix If a favorable subjective response was obtained nd if residual urine volume did not exceed 150 cc he patient was considered to be favorable for uni ateral infravesical partial nerve resection He em loyed the operation 32 times for various types of rinary incontinence including urge incontinence nfectious incontinence including interstitial cysti is uninhibited neurogenic bladders eneuresis cerebral lesions including multiple sclerosis and myelomeningocele In retrospect Ingelman Sundberg considered the main indication for the operation was for patients with uninhibited neurogenic bladders and suggested that the other conditions could probably be best managed by specific anti cholinergic drug therapy

In preparing an article for this Ingelman Sundberg s Festschrift in honor of his many years of service as Editor for Acta Obstet Gynecol Scand I have chosen to report my results on the operation of partial resection of the infravesical nerves for urinary incontinence caused by detrusor dyssynergia (2) as portrayed by direct electronic urethrocystometry

Direct electronic urethrocystometry was first reported in 1963 by Hodgkinson & Cobert (2) The technique was devised to continuously monitor bladder and urethral pressures as the bladder naturally filled with urine from the time the bladder was empty until it became subjectively full

To test for bladder irritability two provocative tests for detrusor dyssynergia are performed The first provocative test is done immediately after the catheters are installed when the bladder is essentially empty To perform this test the patient is asked to stand erect She is then asked to forcibly cough 3 times at 30 second intervals Following coughing she is then asked to stand on her toes and forceably jounce downward on her heels on 3 separate occasions at 30 second intervals She is then placed flat on the table allowing the bladder to fill naturally and she is asked to report when she experiences a natural sense of urgency to void At this time the second provocative test similar to the first is performed Following this she enters the bathroom and behind the closed door is asked to

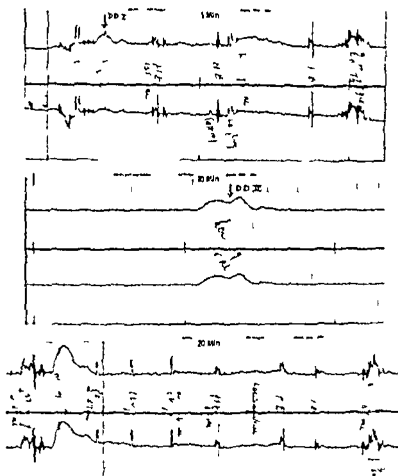


Fig 1 In all frames the upper tracing represents intravesical pressure and the lower tracing mid urethral pressure

Detrusor Dyssynergia Types I and II Type I Detrusor Dyssynergia is an uncontrollable detrusor contraction provoked by some skeletal muscle activity such as coughing Type II is an uncontrollable detrusor contraction occurring spontaneously without skeletal muscle activity It is apparently provoked when the bladder urine reaches a certain critical volume peculiar to each patient (Indicated by arrows)

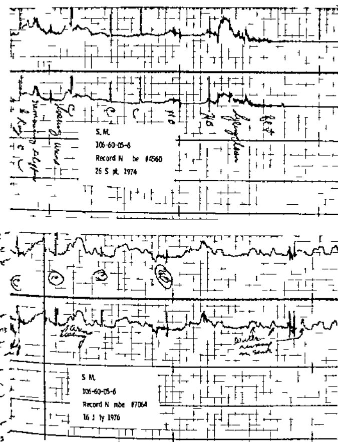
void During voiding the pressures in the bladder and urethra are recorded After voiding the volume of residual urine and the total bladder capacity are measured

Using this simple technique several basic observations fundamental to normal urinary control were observed *First* it was observed that in normal continent women there is no increase in either bladder or mid urethral pressure from the time the bladder is empty until it is subjectively full *Second* no detrusor contractions can be provoked by coughing or jouncing on the heels indicating complete suppression of detrusor auto contractility *Third* increases in intra abdominal pressure induced by coughing are directly transmitted to the bladder and mid urethra *Fourth* the sensation to void is incidental to bladder urinary volume and not to increased intra vesical pressure

The above conditions always prevail in normal adult females as well as in patients with anatomic stress urinary incontinence However in the screening of women complaining of urinary incontinence a certain number were discovered to be losing urine incidental to abnormal detrusor contractions Because the uninhibited detrusor contractions resembled those observed in patients with neurologic bladders intensive neurologic investigations were performed In a small per entage of cases a definite neurologic deficit was detected These patients were assigned to a category of neurologic disease and were excluded from the study The vast majority of pati nts observed to lose urine because of uninhibited bladder contractions were proven to be free of both neurologic and urologic disease Because of this they were assigned to a diagnosis of detrusor dyssy[nergia] of unknown etiology

IDIOPATHIC DETRUSOR DYSSYNERGIA

Continued study of this group of patients has suggested the following observations



Figs 2–3 Patient S M was first observed in 1974 with mild and usually controllable detrusor dyssynergia Types I and II She gained some relief with anticholinergic drug therapy However her disability gradually increased to the point where she was constantly soaking wet Repeat direct electronic urethrocystometric study performed in 1976 (Fig 3) showed marked increase in the degree of detrusor dyssynergia

Detrusor dyssynergia as disclosed by direct ...tronic urethrocystometry is manifest as two ...s Type I is an uncontrallable detrusor contrac... occurring as the result of some skeletal muscle ...vity such as coughing or jouncing on the heels ...e evidence in provocative tests 1 and 2 (Fig 1) ...ype II detrusor dyssynergia occurs as a ...ntaneous unprovoked detrusor contraction ...en the patient is lying flat on the table It appears ...a crescendo-diminuendo type of smooth muscle ...traction producing a pressure rise in both the ...dder and mid urethral leads The increased pres... reaction causes a spontaneous flow of a small ...ount of urine (50–100 cc) The detrusor contrac... is apparently triggered by a critical bladder ...e volume Once the contraction ceases bladder ...tability again subsides until the critical volume is ...ain reached when the detrusor contraction again ...urs This sequence is repeated at regular inter...ls so long as the bladder and urethral pressures ... recorded (Fig 1)

2 Detrusor Dyssynergia both types I and II are purely motor phenomena because a sense of urgency to void never accompanies the urine loss

3 It appears likely that detrusor dyssynergia is a condition peculiar to women if males lose urine on the basis of abnormal detrusor contractions some neurologic abnormality can usually be assigned

4 In patients with detrusor dyssynergia certain pathologic urologic manifestations may be present persistent residual volumes of 75 to 150 cc are usually present on cystoscopic examination fine trabeculations of the bladder are usually evident This latter observations has at times led to the diagnosis of vesico-urethral obstruction On this basis sometimes vesical neck resection has been performed at times this has led to complete urinary incontinence

5 Patients with detrusor dyssynergia usually increase in severity with the passage of time (Figs 2 and 3)

6 About 50% of patients with detrusor dyssynergia are responsive to anticholinergic drugs such as Propantheline (Probanthine Searle and

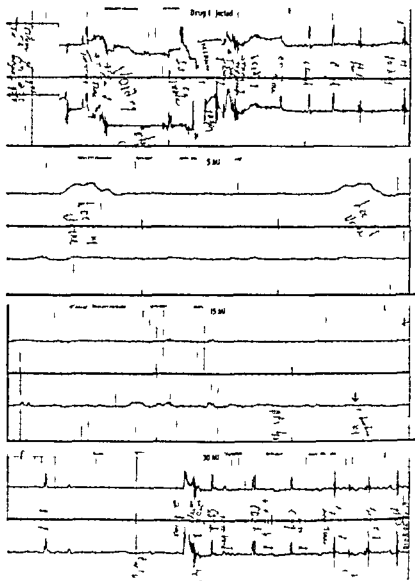


Fig 4 Detrusor dyssy[illegible] I and II completely responsive to Probanthine 15 mg I V The time injection is indicated by the arrow Note complete freedom of detrusor contractions during provocative no 2 in the bottom frame (The urethral lead failed to function adequately during this test)

Company Chicago Ill) Such patients can frequently be managed by oral medication with establishment of excellent urinary control (Fig 4)

7 About 50% of patients with detrusor dyssynergia respond poorly or not at all to anticholinergic drugs These are the patients for whom the operation of Ingelman Sundberg resection of the infravesical nerves may be considered

DIRECT ELECTRONIC URETHRO VESICAL CYSTOMETRY AND DETRUSOR DYSSYNERGIA

Although Ingelman Sundberg advantageously employed retrograde standard water cystometry continuously recorded for the study of his cases direct electronic urethrocystometry has been shown to have many advantages Although standard water cystometry and the newly introduced explosive gas cystometry will provoke the unstable bladder muscle to vigorously contract neither of the methods are sufficiently discriminative to differentiate bladder instability incidental to cystitis nerve dysfunction muscle dysfunction and psychogenic bladder dysfunction

In patients discovered to be losing urine because of detrusor dyssynergia the following investigative procedure is followed at Henry Ford Hospital

1 The patient is referred to the neurologist for a comprehensive neurologic examination If a

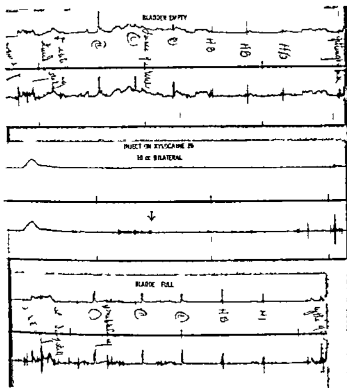


Fig 5 Detrusor dyssynergia Types I and II Injection of 1% Diethylaminoacet 2 6-xyladide with 0 0005% epinephrine 10 cc bilaterally 1 cm lateral to the cervix 3 cm depth (indicated by arrow) Note complete suppression of detrusor contractions subsequent to time of injection (Preoperative to partial infravesical nerve resection Same patient as in Fig 6)

rologic deficit is discovered investigative pro-
tures are continued

The patient is referred for comprehensive logic investigation If no specific urologic lesion iscovered investigation is continued

With the above two studies declared negative peat direct electronic urethrocystometric study erformed The test is allowed to continue until ntaneous detrusor pressure contractions are erved At this time the patient is tested to de mine her reaction to an anti cholinergic drug pantheline 15–30 mg is injected intravenously If patient responds the investigation is stopped d she is given a trial with oral anti cholinergic ugs Propantheline Bromide (Probanthine Scarle d Company Chicago Ill) Imipramine Hy Y) and Sodium Diphenylhydantoin (Dilantin rke Davis Company Detroit) If a favorable clin al response is obtained an appropriate dosage hedule is worked out and no additional treatment necessary (Fig 4)

4 If the patient fails to respond to anticholin ic drugs the direct electronic urethrocystometric test is again repeated Once the detrusor contractions have been observed to occur an injection is made of 10 cc of 1% Diethylaminoacet 2 6-xyladide with 0 0005 epinephrine 1 cm supero-lateral to the cervix at a depth of 2 to 3 cm If the patient is responsive to local anesthesia the abnormal detrusor contractions will be immediately suppressed (Fig 5) Patients who respond in this fashion are considered to be candidates for partial infravesical nerve resection

Although patients who have been properly investigated will usually obtain an excellent response to infra vesical nerve resection it must be remembered that the operation is purely empirical In the occasional patient the operation will fail completely while in others it will be completely successful Occasionally the relief obtained by the operation will be variable and at other times an initially successful operation will be followed by gradual recurrence For these reasons a complete explanation of the possible results must be given to the patient beforehand and the decision to have the operation must be entirely hers Usually however patients with detrusor dyssynergia have been so

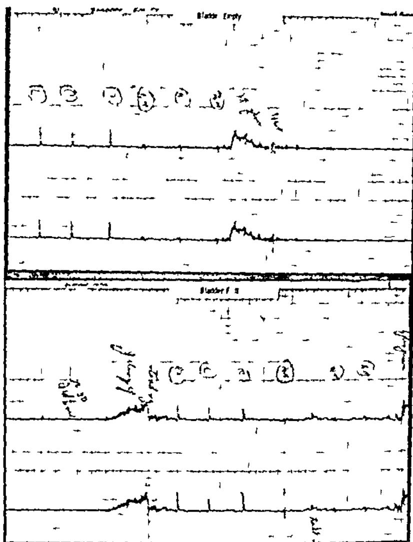


Fig 6 Detrusor dyssynergia Type I and II 10 days post-operative to partial resection of infravesical nerves bilateral (same patient as Fig 5) This operation was performed in 1976 she has enjoyed normal bladder control sin... absence of abnormal contractions

miserable for so many years that they are willing to ...sk the chance of failure

OPERATION

1 A circumlinear horseshoe shaped incision as recommended by Ingelman Sundberg is made through the mucosa of the anterior vaginal wall extending forward from each lateral vaginal fornix to join at a point about 4 cm posterior to the external urethral meatus (Fig 7)

2 The anterior vaginal mucosa is dissected free posteriorly to the level of the cervix

3 The tissue lateral to the cervix between the vesical ligaments and the pubococcygeus muscles are dissected free in an antero-posterior direction by opening and closing long thin bladed tissue forceps or narrow bladed scissors

4 Long narrow bladed retractors are inserted to the level of the cervix upward and lateral traction usually discloses strands of whitish nerve fibers ascending ... with the inferior vesical artery The combined nerve artery bundle averages 4 to 5 mm in diameter (Fig 8)

5 With the artery nerve bundle exposed for a distance of about 3 cm clamps are applied leaving an intervening artery nerve bundle of about 2 cm the intervening artery nerve bundle is excised and sent to the laboratory for nerve identification We prefer to tie the clamped artery nerve bundle ends with polyglycolic acid ligature no 3 9 although Ingelman Sundberg used coagulation cautery

6 If the procedure is to be performed bilaterally the opposite side is similarly dissected

7 With the bleeding controlled the edges of the vaginal mucosa are approximated with continuous locking ... 3-0 polyglycolic acid suture

8 Continuous bladder drainage is established by ... ing a suprapubic cystostomy Bonanno catheter After ... days the catheter is clamped and initiation of voiding ... instituted



7 Curvilinear incision in the anterior vaginal mucosa the two posterior arms of the incision extending over lateral vaginal walls near the level of the cervix

Once voiding is well established usually by the 4th operative day the bladder tonus is again tested by electronic urethrocystometry A successful opera is indicated by complete suppression of all abnormal trusor dyssynergia contractions both Types I and II 6)

RESULTS

Although Ingelman Sundberg employed the opera for various kinds of urinary incontinence in cluding urgency incontinence infectious inconti nence and eneuresis he gradually restricted indica tions for the procedure to patients with uninhibited neurogenic bladders

At Henry Ford Hospital the procedure has been used only for patients disclosed to have severe de trusor dyssynergia Types I and II as evident on electronic urethrocystometry Over the past 14 years 23 patients have been subjected to partial infravesical nerve resection They ranged in age from 37 to 84 years with the average age 52 All patients but 3 have been followed for more than 1 year

In 7 patients the operation was a complete failure In 4 patients substantial relief was obtained but occasional urinary incontinence occurred if they allowed their bladders to become excessively full or if they developed urinary tract infection Two pa tients were apparently cured initially but after 1 year showed evidence of gradual recurrence of de trusor dysfunction of a relatively minor degree In 1 patient there was an apparent immediate failure but after several months she gradually improved and presently has quite satisfactory urinary control In cidentally this last mentioned patient was a teen aged daughter who has been shown to have de trusor dyssynergia Types I and II The remaining 12 patients are apparently cured Direct electronic urethrocystometric studies have indicated that of the 3 patients followed for less than one year 2 are cured and one is substantially improved

CONCLUSIONS

Although partial infravesical nerve resection is empiric operative procedure for patients with idiopathic detrusor dyssynergia it may be the only means of offering hope for a condition which is otherwise incurable To Ingelman Sundberg must go credit for his genius in rationalizing the idea and for his skill in devising the surgical technique

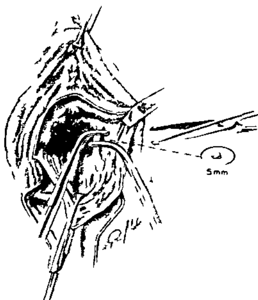


Fig 8 Exposure of the artery nerve bundle lateral to the cervix Each nerve bundle is doubly clamped leaving a 3 cm intervening segment the nerve bundle is cut and the intervening segment sent to the laboratory for microscopic identification of nerve bundles

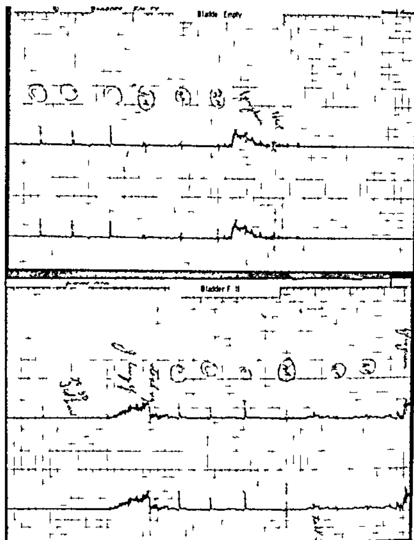


Fig 6 Detrusor dyssynergia Ty[...] I and II 10 days post-operative a[...] partial resection of infravesical nerves bilateral (same patient as Fig 5) This operation was performed in 1976 she has enjo[...] normal bladder control since M[...] absence of abnormal contraction

miserable for so many years that they are willing to risk the chance of failure

OPERATION

1 A circumlinear horseshoe shaped incision as recommended by Ingelman Sundberg is made through the mucosa of the anterior vaginal wall extending forward from each lateral vaginal fornix to join at a point about 4 cm posterior to the external urethral meatus (Fig 7)

2 The anterior vaginal mucosa is dissected free posteriorly to the level of the cervix

3 The tissue lateral to the cervix between the vesical ligaments and the pubococcygeus muscles are dissected free in an antero-posterior direction by opening and closing long thin bladed tissue forceps or narrow bladed scissors

4 Long narrow bladed retractors are inserted to the level of the cervix upward and lateral traction usually discloses strands of whitish nerve fibers ascending upw[...] with the inferior vesical artery The combined ner[...] artery bundle averages 4 to 5 mm in diameter (Fig 8)

5 With the artery nerve bundle exposed for a dista[...] of about 3 cm clamps are applied leaving an interven[...] artery nerve bundle of about ? cm the interven[...] artery nerve bundle is excised and sent to the laborat[...] for nerve identification We prefer to tie the clamp[...] artery nerve bundle ends with polyglycolic acid ligatu[...] no 3 9 although Ingelman Sundberg used coagulat[...] cautery

6 If the procedure is to be performed bilaterally [...] opposite side is similarly dissected

7 With the bleeding controlled the edges of the vagi[...] mucosa are approximated with continuous locking [...] 3-0 polyglycolic acid suture

8 Continuous bladder drainage is established by inse[...] ing a suprapubic cystostomy Bonanno catheter Afte[...] days the catheter is clamped and initiation of voiding [...] instituted

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RESULTS OF OPERATIVE TREATMENT OF STRESS URINARY INCONTINENCE WITH SPECIAL REFERENCE TO PREOPERATIVE CLINICAL AND RADIOLOGICAL EVALUATION

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tract Operative results of stress urinary incontinence discussed on the basis of a follow up study made 3–5 r after the operation The series consisted of 301 ients operated on during 1969–1971 The most signifi t anamnestic feature was the great number of mul ras 67% of the patients had given birth to at least hildren The choice of the operative method was based Green s urethrocystographic classification into type I l type II The healing was complete or satisfactory in % of the total material In the group operated on ac ding to type I the outcome was good in 88% while in type II group it was good in 84% Incontinence of pee I was cured in 89% of the cases while patients of pee III in only 72% If there was a significant urgency nponent observable in the incontinence symptoms operatively a good outcome was only attained in 64% pure or dominant stress incontinence the corresponding come was 88% Hysterectomy combined to the opera n seemed to improve the results Age parity duration the incontinence symptoms weight and changes of ight after the operation had no significant effect on the aling The authors emphasize the importance of careful ferential diagnosis based on the anamnesis and exami tions in choosing the therapeutic method for inconti nce patients

te etiology of stress urinary incontinence is attri ted to weakened supportive structure of the lvic floor which results in a disappearance of the sterior urethrovesical angle and a change in the rection of the urethral axis during straining odgkinson (9) postulated stress incontinence as ing mainly due to a descent of the proximal por on of the urethra into a more caudal position than ormal whereupon it can no longer resist the in reased hydraulic intravesical pressure According Hutch (10) the low position of the basal plate of e bladder leads to a partially open internal orifice of the urethra which results in a decline in urethral resistance As a consequence of these anatomical changes the even application of the intra abdominal pressure wave on the urethra is prevented Intravesical pressure thus exceeds the intraurethral pressure and urine escapes upon straining (3)

In differential diagnostics stress incontinence should first of all be distinguished from urgency incontinence which frequently has a background of infections as well as mucosal atrophies A psychosomatic and neurological background is also often noted This type of incontinence should be corrected conservatively

The results obtained by operative treatment of stress incontinence vary greatly Using the vaginal operation (14 15) the cure rates have been between 50–77% (13 18) Ingelman Sundberg (11) pointed out that recidivous cases are common after the Kelly–Kennedy operation the pubo-coccygeoplasty developed by him resulted in recovery in 94% of the cases and distinct alleviation of symptoms in 6% The results obtained from suprapubic vesicourethral suspension (16) are variable from 65% to 98% (4 6 17)

The 266 patients with urinary incontinence operated at the Department of Obstetrics and Gynecology University of Oulu during 1965–1967 were analyzed previously (12) A follow up examination made 3–5 years after the operation showed 57% patients to be fully asymptomatic and 28% to suffer from merely mild incontinence In 1968 we adopted the method of Green (5) for choosing the operative technique on the basis of bead chain urethrocystography findings Type I includes the

Table I *Distribution according to age groups*

<30		30–39		40–49		50–59		≥60	
N	%	N	%	N	%	N	%	N	%
5	2	42	14	116	38	110	37	28	9

patients in whom the posterior urethrovesical angle is straightened upon straining but the urethral inclination angle remains smaller than 45 In type II the inclination angle becomes greater than 45 The type I patients are operated on via the vaginal route (Kelly–Kennedy plastic) (14 15) In type II suprapubic suspension of the vesical neck and the urethra is accomplished with the Marshall–Marchetti–Krantz operation (16) The value of anamnestic data in accurate preoperative differential diagnosis of urinary incontinence has been emphasized

The purpose of this follow up study is to present the results of the operative treatment of incontinence patients taking into account the choice of the type of operation the severity of incontinence and the preoperative nature of the incontinence

MATERIAL AND METHODS

During the years 1969–1971 301 patients with urinary incontinence were operated on at the Department of Obstetrics and Gynecology University of Oulu The mean age of the patients at the time of the operation was 48 4±8 5 years (Table I) and 75% of them belonged to the age group of 40–59 years The patients had had an average of 5 1±2 9 deliveries before the operation (Table II) 67% of them had had 4 or more deliveries and 10% belonged to the group of 10 or more deliveries The average duration of the symptoms of urinary incontinence before the opera n was 7 9±7 4 years Concurrent uterovaginal prolapse noted in 229 patients (76%) The mean weight at the e of operation was 68 4±10 kg 250 patients (83%) had an occupation requiring manual work 150 (50%) had been delivered of at least one child weighing over 4 kg 25 (8%) had had a vacuum extraction or forceps delivery Recidivous urinary tract infections had been suffered preoperatively by 126 subjects (42%) The symptoms of 220 (73%) had appeared before menopause 15 patients (5%) had previously been operated on because of urinary incontinence The grading of incontinence is presented in Table III 56% of the present series belonged to grades II or III The anamnestic classification of the patients according to type of incontinence shows that 274 (91%) had pure stress incontinence or a mixed type of incontinence dominated by stress symptoms 27 (9%) had urgency symptoms dominating over the stress symptoms They were operated on because of concurrent uterovaginal prolapse or a failure of conservative treatment

84 patients (27%) underwent a vaginal Kelly Kennedy operation sometimes combined with vaginal hysterectomy (Table IV) The Marshall–Marchetti–Krantz operation either alone or in combination with various vaginal or abdominal measures was used in Green's group II (72%) Three patients underwent a sling operation

The average period between the operation and the follow up examination was 47±8 months 9 patients (97%) participated in the follow up personally while 3 did so by a letter 98 patients with continuing incontinence symptoms were subjected to cystometry at the follow-up examination

RESULTS

The effect of the operative methods on the results

85% of the patients had become entirely free from incontinence and 30% had recovered enough not to have daily inconvenience (Table V) The overall percentage of recovery is hence 85% The mean time between the operation and the appearance of recidivous symptoms of incontinence was 11 8+11 months The operation for Green's type I resulted in healing in 88% (Table V) the corresponding value for type II being 84% Additional hysterectomy improved the results (Table VI) If the type of operation was a pure Marshall–Marchetti–Krantz suspension the results was evaluated as cured or improved in only 64% Combinating the MMK operation with abdominal hysterectomy the corresponding value was 66% If the MMK operation was performed with vaginal raphies or vaginal hysterectomy a good operativ result was achieved in 86% For 14 patients (5%) the outcome of the prolapse operation was nonsatisfactory This had no effect on the healing of urinary incontinence

The effect of other factors on the results

Urinary incontinence was healed in 89% of the patients with grade I incontinence 84% of the grade II patients and only 72% of the grade III patients (Table VII) The differences are not significant ($p<0.05$) however 88% of the patients with pure or dominant stress incontinence recovered while only 64% of those with urgency symp-

Table II *Distribution according to parity groups*

0		1–3		4–6		7–9		≥10	
N	%	N	%	N	%	N	%	N	%
7	2	94	31	118	39	51	17	30	10

able III *Classification of urinary incontinence*

ade		N	%
I	Urine leaks when coughing	132	44
I	Urine leaks when walking	145	48
I	Urine leaks even at lying	24	8

ms dominating preoperatively did so (Table VIII) his difference is highly significant ($p<0.001$)

The following factors on the other hand had no fect on the results age at the time of the opera on parity preoperative duration of urinary incon nence and weight at the time of the operation or hange of weight after it

Recidivous urinary infections had been suffered ostoperatively by 104 patients (35%)

omparison of pre and postoperative continence

his comparison also includes the cases where the continence was not completely cured by the oper tion though it did not cause daily inconvenience Table IX) 61% of the cases classified as pure tress incontinence preoperatively came symptom ss but 13% developed incontinence dominated y urgency symptoms In the cases where urgency ymptoms dominated preoperatively a good opera ve outcome was obtained in 26% but 61% con nued to have mild or severe urgency symptoms

esults of postoperative cystometry

The findings of the 98 follow up examinations are resented in Table X where the results are com ared according to the type of postoperative incon nence Even those with mild postoperative incon nence are included The bladder volume was be

Table IV *The operative methods used*

Method	N	%	
Vaginal raphies or Manchester+Kelly	58	19	27
Vaginal hysterectomy+Kelly	24	8	
Marshall–Marchetti–Krantz (MMK)	48	16	72
Abdominal hysterectomy+MMK	48	16	
Vaginal raphies+MMK	72	24	
Vaginal raphies+abdominal hysterectomy+MMK	33	11	
Vaginal hysterectomy+MMK	15	5	
Sling-operation	3	1	

Table V *Results of operative treatment by different methods*

Postoperative course	Vaginal N	Vaginal %	Suprapubic N	Suprapubic %	Total N	Total %	
Cured	71	88	185	84	166	55	85
Improved					90	30	
No change	10	12	35	16	37	12	
Worse					8	3	

low 300 ml in 20% of the patients with urgency symptoms dominating the postoperative clinical picture The corresponding proportion of patients with stress incontinence was only 4% Increases of intravesical pressures exceeding 5 cm H_2O upon 300 ml filling were recorded for 65% of the patients with urgency incontinence Pain on filling with less than 300 ml was more than twice as common in the subjects with urgency symptoms as in those with stress symptoms at the follow up examinations

DISCUSSION

The present series was characterized by high parity values and severity of preoperative incontinence Stress incontinence is mainly due to anatomical weakness of the muscle of the pelvic floor which is primarily attributable to pregnancies The proportion of multiparas in series of stress incontinence has previously been found to vary within 95–97% (5 12) The present series only included 7 nulliparas while 2/3 had 4 or more deliveries and nearly 1/3 had 7 or more The parity rates do not however correlate with the recovery figures The preoperative severity grade of urinary incontinence was estimated as II or III in 56% of the cases This series hence represented more serious incontinence

Table VI *Effect of the combination of hysterectomy with the incontinence operation on the results*

	With hysterectomy N	With hysterectomy %	Without hysterectomy N	Without hysterectomy %
Cured or improved	108	89	148	82
No change or worse	13	11	32	18

Table VII *Effect of degree of urinary stress incontinence on the results*

	Grade					
	I		II		III	
	N	%	*N*	%	*N*	%
Cured or improved	117	*89*	121	*84*	18	*72*
No change or worse	15	11	23	16	7	28

Table VIII *Effect of the preoperative urgency symptoms on the recovery rate*

	No urgency		Significant urgency	
	N	%	N	%
Cured or improved	230	*88*	25	*64*
No change or worse	31	12	14	36

Table IX *Relations between pre and postoperative incontinence*

	Preoperative incontinence			
Postoperative incontinence	*Stress*		Significant *urgency*	
	N	%	*N*	%
No incontinence	159	*61*	10	*26*
Stress	69	*26*	*5*	13
Significant urgency	*34*	*13*	*24*	*61*

than the previous series from the same clinic (12) The preoperative severity grade correlated with the outcome of operation although the differences were non significant

The present results agree with those presented by Green (7) as regards both the distribution of the patients into type I and type II and the operative results obtained in these groups Only 77% of the present patients belonged to group I 88% of them recovered well while 84% of the patients with suprapubic operation had an equally good outcome The corresponding values reported by Green (7) were 95% and 91% Bailey (?) and Green (7) have maintained that a vaginal operation leads to healing in only about 50% of the type II cases Our results show also that operative results of vesicourethral suspension (Marshall–Marchetti–Krantz) can be improved by simultaneous raphies or hysterectomy which agrees with earlier observations (6) Combination of hysterectomy with the incontinence operation seemed to improve the results which agrees with the previous observations (7 12)

According to the present findings the operation eliminated the symptoms of incontinence patients either entirely or to a clinically insignificant level in 85% of the cases which is in full our earlier results (17) Green s classification (5), which was adopted into use in our clinic this had no improving effect compared with the previous series Our results were not equally good as reported by the others either Green (7) reported healing in 96% McGuire et al (17) in 9?% What could be the reason for these differences? In the present series the preoperative differential nosis of incontinence had been based mainly on the anamnesis and no cystometric studies or cystoscopy had been performed systematically In the series of McGuire et al (17) the operation had been preceded by careful urodynamic investigations The present series included 9% of patients diagnosed to have dominantly urgency incontinence

Table X *Relation between the nature of postoperative incontinence and the some cystometric findings (98 cystometric examinations)*

	Volume of urinary bladder				Increase of intravesical pressure at 300 ml				Bladder volume at the appearance of pain			
	≥300 ml		<300 ml		<5 H_2O cm		≥5 H_2O cm		≥300 ml or no pain		<300 ml	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Stress	50	96	2	4	32	67	70	38	40	77	[illegible]	[illegible]
Significant urgency	47	80	9	70	16	35	30	65	22	48	[illegible]	[illegible]

operatively Only 64% of these had a good out ne which impaired the results of the total series % of the cases with pure or dominant stress in ntinence had a good outcome Th s difference s highly significant (p<0 001) On the other nd 13% of those with dominantly stress symp ns preoperatively turned out to have a domi nce of urgency symptoms after the operation e reason for this may be that the preoperative amnesis did not reveal the urgency symptoms uch only appeared after the stress incontinence d been corrected operatively The irritation of the trusor muscle or the urethra by the operation or high frequency (35%) of postoperative recidiv d urinary infections may also contribute to this

The results here obtained emphasize the great e to be taken in the preoperative differential gnosis of incontinence patients Our clinic has in last few years introduced a questionnaire which ves to differentiate accurately between the dif ent types of incontinence Routine cystoscopy d cystometric studies have also been taken in operative praxis Special attention should be di ted to the detrusor dyssynergy symptom (1 8) is type of incontinence is regarded as represent the form of urinary incontinence second in fre ency It is due to involuntary activity of the de sor muscle which is characterized by appear ce of incontinence a short time after the eleva n of intra abdominal pressure This type of in ntinence which should be treated conservatively ay be confused with stress incontinence We tend to continue using the current operative ethods in the future but will try to render the operative differential diagnosis of incontinence ter more reliable

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PREREQUISITES FOR TUBOPLASTY

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ract Techniques in measuring tubal patency and pretation of findings can be misleading Laparoscopic y of infertile women with suspected diseased fal n tubes is always prerequisite to tuboplasty Ob ations must be accompanied by intrauterine injection dequate amounts of dye and gentle tubal manipula s Determined efforts should be made to eliminate nstructive operations on nonsalvageable tubes be se successful term pregnancies following tuboplasties related more to the extent of tubal damage than to rative technique or postoperative management

any infertile women with diseased Fallopian bes do not have tuboplasty because of contra dications existing such as age a history of pelvic berculosis obesity or a recent adnexal infection ith residual pelvic tenderness Infertility studies ay reveal seminal inadequacy poor sperm migra on or ovular dysfunction When the limited an es of success are described some women re se operations In a report by Murray (1) on 2 148 fertile women 311 (14 5%) were operated upon nd of these 86 had tuboplasty Crane & Wood (2) reporting their experiences with 96 tubo lasties maintained that the properly selected pa e and extent of periadnexal adhesive disease ally influenced prognosis O Brien and col eag es (3) reviewed 173 tuboplastic operations of them on private patients followed by a 35% regnancy rate Of 1 126 clinic patients seen during 10-year period for infertility 424 (37%) had tubal disease but only 11? came for reconstructive sur ery

The incidence of tubal disease reported as a cause of sterility in any series varies with the type of patients studied Peterson & Behrman (4) noted that 5% of women with unexplained infertility had subsequent tubal pathology at laparoscopy Corson & Bolognese (5) found tubal disease in 145 (58%) of 249 patients undergoing laparoscopy for infer tility

The results from conventional nonoperative tests for tubal patency uterotubal insufflation and hys terosalpingography may be misleading because of the inherent limitations of these procedures The results also depend upon the physicians technique and interpretation A presumptive diagnosis of tubal occlusion during insufflation can be made if passage of carbon dioxide does not occur below 200 mmHg kymographic oscillations are absent and no shoulder pain follows the test Of 500 in fertile women who eventually became pregnant Rubin (6) noted initial pressures of 200 mmHg on one or two occasions in only 12 patients (2 4%) but none conceived after three negative tests In a similar group of 296 infertile women Siegler (7) found only one patient who conceived after three negative tests These observations suggest that reported failure of carbon dioxide to pass through Fallopian tubes is indeed a poor prognostic sign Uterotubal insufflation is not too accurate in the presence of dilated occluded ampullae resulting occasionally in misleading or false positive tests

Salpingography can show the size of a distal tubal obstruction but not the condition of fimbriae the degree of tubal fixation or endosalpingeal de struction Persistent localized collections observed on the follow up X ray film suggest ampullary disease Boyd & Holt (8) made a diagnosis of hydro salpinx by hysterosalpingography in 130 instances and a subsequent laparotomy disclosed only four normal (3 1%) patent tubes Hysterosalpingo graphic interpretations of distal obstruction without dilatation is less accurate because at laparoscopy many tubes show patency but are restricted by peri tubal adhesions Young and colleagues (9) per

formed tuboplasties on 112 infertile clinic patients confirming the observations of Özaras (10) who correlated postoperative pregnancy rates following salpingoneostomy with preoperative radiologic rugal markings Their presence indicated minimal endosalpingeal disease 60% of the patients conceiving after tuboplasty while in their absence only 7% became pregnant

Swolin & Rozencrantz (11) compared findings of laparoscopy and hysterosalpingography in 143 patients both methods being in agreement in the diagnosis of partial or complete tubal obstruction and tubal adhesions in 90 women (63%) Significant tubal abnormalities differing in degree were seen with both techniques in 24 other patients (17%) Normal laparoscopic findings were found in 14 women whose hysterosalpingograms were interpreted as abnormal Bilateral tubal patency was detected in a previous hysterosalpingogram in 12 patients although partial obstruction was noted on laparoscopy Radiologic studies were performed before ovulation with water soluble media followed the next day by laparoscopy using methylene blue or indigo carmine with saline Maathius and colleagues (12) and Coltart (13) found in comparing the results of hysterosalpingography and laparoscopy that most errors occurred because detection of significant peritubal adhesions cannot be made by radiologic techniques Results from insufflation and salpingography should be carefully interpreted but it is sometimes difficult to evaluate the extent of tubal abnormalities without endoscopy Although Frangenheim (14) who no longer advocates hysterosalpingography in infertile women he does advise laparoscopy to evaluate the pelvis and has recommended tuboplasty in almost one third of his patients

In bilateral cornual blockage contrast fluid does not fill the tubes and none is seen in the peritoneal cavity on the delayed film In these patients it is important to record the amount of fluid used the degree of leakage at the cervic the force and resistance to the instillation and the patients complaint of pain Careful search for intramural and isthmic filling is important because their demonstration can influence the selection of the type of tubal reconstruction With laparoscopy the tubal isthmus can be palpated to search for the characteristic nodularity of salpingitis isthmica nodosa fimbriae can be manipulated and observed ostia can be probed and tubal patency can be tested by injecting dilute solutions of dye through the cervix Steptoe (15) ad[illegible] laparoscopy in infertile patients to verify tub[illegible] tency with hydrotubation to assess [illegible] tion and fimbrial involvement to evalu[illegible] for possible tuboplasty and to lyse peritubal adh[illegible] sions Operative descriptions are dictated [illegible] rately following the procedure according to an or ganized plan so that important intormation is n[illegible] forgotten Rarely endoscopic observations are mis leading or difficult to interpret and an occasion[illegible] unnecessary laparotomy is done

Congenital or inflammatory luminal fibrosis a[illegible] salpingitis isthmica nodosa are the most commo[illegible] causes for organic proximal obstruction The co[illegible] dition is suspected if 1) nonpatency to CO insuffla tion occurs at 200 mmHg for 2 min at a flow rate [illegible] 30 ml per minute with increasing suprapubic med[illegible] pain but no subsequent shoulder pain 2) opacifica tion of no more than 2 to 3 cm of the fallopian tube is seen after adequate amounts of contrast med[illegible] have been injected without subsequent dispersion 3) at laparoscopy occasional blanching of the isth mic segment is seen with resistance to the injectio[illegible] of dye through the cervical cannula and some va[illegible] inal reflux Tuboplasty is feasible if distal segment[illegible] including fimbriae are normal Isthmic filling of i[illegible] digo carmine in grossly normal tubes without [illegible] usually indicates insufficient dye rather than [illegible] tubal blockage The exact site of occlusion in th[illegible] area may be difficult to locate but occasionally [illegible] mic distention and blanching are seen proximal [illegible] the obstruction Salpingitis isthmica nodosa ca[illegible] missed on hysterosalpingography and laparos[illegible] unless careful observations are made Pal[illegible] manipulation of the tubal isthmus with a [illegible] proble are essential Laparoscopy is prerequisite [illegible] tuboplasty in patients who have cornual or multiple blockage on radiologic studies because the con[illegible] tion of the distal tubal segments is unknown [illegible] laparotomy intrauterine fundal injections of dye a[illegible] attempted to prove obstruction before tubal tra[illegible] section and anastomosis or implantation [illegible] casionally this maneuver causes tubal filling d[illegible] spite previous studies indicating cornual obstru[illegible] tion Even with final corroboration showing b[illegible] lateral occlusion subsequent examinations of e[illegible] cised segments may not reveal any abnormal [illegible] Boyd & Holt (8) reported 34% of tubal [illegible] from such patients examined histologically pro[illegible] normal

In a patient desirous of reversing a tubal ster[illegible]

operation laparoscopy can verify the presence
distal tubal segment evaluate the gross appear
e of the fimbriated end and enable the gyne
gist to ascertain the feasibility of tubal recon
ction

eferred increasing lower quadrant pains during
insufflation suggest ampullary obstruction
degree of distension and character of mucosal
ls can be seen on hysterosalpingography large
mild dilatations without luminal markings being
oor prognostic sign Ozaras (10) found that only
8 patients who had slight dilatation and linear
cosal markings conceived after ampullary sal
e neostomy If ampullary disease is associated
h salpingitis isthmica nodosa tuboplasty is
traindicated Rigid luminal contours indicate
onic advanced salpingitis with fibrosis possibly
gestive of tuberculous salpingitis

At laparoscopy in prefimbrial phimosis caused
endosalpingeal ampullary adhesions free fim
e are noted with tubal filling some dilatation
minimal spill of dye In the absence of peri
al adhesions these problems can be treated by
rotubation In some patients in whom preg
cy still does not occur following ovarian wedge
ection despite successful correction of anovu
on laparoscopic examination is indicated to
rch for the extent of postoperative peritubal ad
sions Relatively normal fimbriae can be ob-
red by adhesions covering the adnexa and pos
ior leaf of the broad ligament Gentle manipula
n probing and cervical instillation of dilute
igo carmine can show tubal patency with ad
sions or distal tubal filling without spill

At laparoscopy chromotubation is indispensable
ecially if terminal tubal segments are fixed firm
in the cul-de sac Tubal filling with only mod
e distention but some spilling of dye in the cul
-sac or behind occlusive adhesions is a favorable
n. A dilated tube with pale thin walls distended
th fluid before instillation of any dye is discerned
ably Additional pathology such as myomas or
an endometriosis indicates a poor prognosis
ss diseased club-shaped distally occluded
bes have a more natural pink color feel less tense
ring probing and fill but do not spill fluid under
paros opic control An occasional hydrosalpinx
to fill with dye during chromotubation rupture
and extravasate material into the mesosalpinx thus
explaining abnormal patency to CO_2 or contrast
medium in some of these patients

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ADVANCES IN TUBOPLASTY

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tract Reconstructive oviductal surgery was per ned on 205 private patients with primary and second infertility who were selected from 1075 endoscopic minations Each patient underwent an infertility sur which included gamete formation reception and de ition of gametes nidation post-coital and semen anal- . Only those with tubal abnormalities not responding conservative therapy after a minimum period of six hs following laparoscopic examination were select for tuboplasty Spiral stents for fimbrioplasty and ight teflon tubing for mid portion and cornua obstruc were employed These stents were removed eight eks post surgery under local anesthesia at the office the 205 tuboplasties 193 patients had sustained pa cy 75 conceived 7 aborted and 1 had an ectopic gnancy Pregnancy occurred between 1 and 26 months r removal of the stents Complications were very few use of Roland spiral teflon stents has resulted in a ater percentage in patency and pregnancy rates as pared to those without use of stents

ADVANCES IN TUBOPLASTY

perience accumulated in the field of infertility onstrates abnormal tubal factors play a role in east one third of all cases and are second only the male factor in incidence Oviductal recon uctive surgery for the restoration of fertility ets with increasing success as experience has n gained Current improvements are based on re discriminating selection of patients by endo- py and modifications of established techniques tical evaluation of certain aspects of technique igned to improve ovum pick up facilitate ga e transportation and expedite zygote passage ough the tube is the subject of this report Sys s for properly selecting candidates for tubo- ty and for reporting the surgery and its results also included in this study

MATERIAL AND METHODS

This presentation is based on the results in reconstruc tive oviductal surgery in 05 patients from our private practice These cases were selected from 1075 endoscopic examinations (48 culdoscopies and 1027 laparoscopies) in patients with primary or secondary infertility Prior to endoscopic examination all patients were evaluated by either our staff or their own gynecologists

Before we subjected any patient to endoscopic exam ination each couple underwent the following office proce dures

Gamete Formation Determined by endometrial biopsy serum progesterone and basal body temperature charts If any of these factors was negative it was repeated in order to establish the positive results

Reception and Deposition of Gametes By means of semen analysis post-coital degree of fern phenomenon and semen penetration tests combination of hydrotuba- tion followed by carbon dioxide insufflation (1) and when indicated hysterosalpingogram

Preparation for Nidation By means of endometrial biopsy serum progesterone (RIA) and basal body tem perature charts This is done premenstrually

Upon the completion of the above procedures and if there existed either the tubal factor or possible ovarian pathology such as Steinoid ovaries and if the latter failed to respond to several months of Clomid therapy these patients should they fail to conceive within a period of six months following the infertility survey and therapy would be subjected to endoscopy Some of these couples had been worked up by other qualified gynecologists and if the survey included all the above mentioned tests and proper therapy used as stated above certified by the abstract received these patients would be admitted to the hospital for endoscopy Most of these patients had laparoscopy and some if indicated also had hystero- scopy at the same sitting It must be pointed out that al most all patients had tried to conceive for periods over two years The only exception would be the elderly nulli parous patient (over 30 years of age) who would be sub- jected to endoscopy at an earlier date for obvious rea sons

Prior to use of endoscopy or stents in a group of 3 patients the postoperative patency result of tubal surgery

Table I *Distribution of results in patients subjected to endoscopy and found to have tubal pathology*

Total number of endoscopies	1 075
Patients with no visible tubal disorders	699
Patients with disorders amenable to correction	317
Patients with contra indications to tuboplasty	39
Patients who refused tubal surgery	14
Patients who conceived after laparoscopy but without tubal surgery (within 6 months)	118
Patients in whom tuboplasty was performed	?05

was only 56% and only 12% achieved pregnancies following tuboplasty without stents Only 6% resulted in live births

Table I illustrates the subsequent course of 376 of the 1 075 patients subjected to endoscopy with presumptive diagnosis of tubal pathology established by the basic evaluation and confirmed by this procedure It is interesting to note that 699 patients of the total endoscopies performed did not reveal tubal pathology to warrant surgery

Table II demonstrates the results of tuboplasty after we adopted the routine use of endoscopy and splinting techniques

Table III lists the time interval between tuboplasty and resulting pregnancy

TUBAL RECONSTRUCTIVE TECHNIQUE

The re anastomosis of previously ligated tubes or mid portion obstruction was performed over a straight teflon splint of narrow calibre with the simple approximation of the freshly transected debrided ends by 5-0 chromic interrupted sutures through the seromuscular coat (? 3) (Fig 1)

Cornual implantation of proximally occluded tubes is carried out by a significant modification of the standard procedure which has proven advantageous The conventional technique creates a large opening with a cork borer and employs a fishtail incision at the cornual end of the oviduct This implantation which is fixed by sutures in the endometrial cavity is followed by healing with the endosalpingeal tissue growing in the cavity of the uterus The large cornual opening in the myometrium and the tubal tissue in the endometrial cavity have proven unphysiological and in some cases have met with disastrous cornual nidation and alarming bleeding at tubal abortion with tubal rupture In contrast we employ a narrow trocar and cannula to establish a uniformly narrow cornual interstitial tract to the endometrial cavity The management of the diseased portion of the tube is also critical It is our concept that the maximum length of the tube must be preserved for physiologic transport of the zygote Therefore to avoid sacrificing an undesirable length of tube we employ a wire probe and simply establish a channel in the proximal portion of the oviduct (?) creating a new lumen In addition we denude one centi meter of the serosa of the proximal portion of the c The straight teflon splint is then introduced through the fimbrial end of the oviduct and on exiting the cornual end is fixed within the endometrial cavity with two 4 chromic sutures on a large curved or straight Keith needl passed obliquely through the cavity and out the serosa c the fundus The serosa of the oviduct is then approxi mated to the serosa of the fundus at the cornual insertion with interrupted 5-0 chromic sutures (Fig ?-4) We be lieve the endosalpingeal epithelium grows over the splin from the tubal side but does not reach the endometri cavity whose epithelium comes to line a part of the in ter stitial portion of the splint We believe this to establish more physiological union of the two epithelia at a mor appropriate junction thus eliminating the impairment t the progression of the blastocyst through the contracted interstitial portion of the tube and permits timely nid tion

Fimbrioplasty which is most commonly called for h been accomplished with dramatic improvement in our re sults by the introduction of the Roland spiral teflon ste as has been previously reported (4 6) The spiral portio of the stent has a cone shaped flare from the straight po tion of the tubing so that it conforms to the shape of th ampullary and fimbriated portion of the oviduct Th teflon tubing is strengthened by a matrix of straight fir copper wiring which is malleable and assumes as well, th shape of the spiral cone The critical features of successful fimbrioplasty include lysis of all adhesions and adequa dilatation of the constricted or occluded abdominal os tium of the oviduct with graduated teflon cones at all times maintaining moistness of the fimbria with saline ir rigation The spiral cone is then inserted in the ampulla with a grooved metal cone shaped guide and is fixed within the ampulla for the duration of healing by placing three or four 4-0 chromic sutures in the serosal coat of the oviduct just proximal to and parallel with the abdominal ostium and tying these over the distal lo of the spiral cone seated deeply in the ampulla (Fig 5)

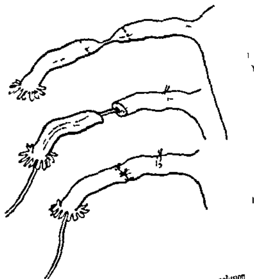


Fig 1 Steps in reconstruction of midportion occlusion

able II *Tuboplasty results in patients in whom pre operative endoscopy and stents were used*

ype of lesion	Total no of patients	Post operative patency No	Post operative patency %	Pregnancy No	Pregnancy %	Abortion* No	Live births* No	Live births* %
ilaterally homogeneous								
Midportion	4	3	75	3	100		3	100
A For reanastomosis	2							
B Midportion occlusion	2							
Cornual	2?	20	91	12	60	1	11	92
Fimbrial	135	129	96	45	35	4	41	91
ilaterally mixed	44	41	93	15	37	?	13	87
otals and %	205	193	94	75	39	7	68	91

[illegible] pregnancies of patent tubes
[illegible] of pregnancies

In all of these procedures employing teflon splints the stal fimbs are each individually passed 2 cm apart rough the layers of the abdomen to exit just beneath e skin The two free ends are tied together in three lefined easily palpable knots and fixed between the arpa s fascia and the skin closure (Fig 6) Eight weeks st-operatively is the appropriate time for removal . It is readily accomplished with minimum discomfort observing the following rules With local anesthetic infiltration a one centimeter incision is made just above the inary Pfannenstiel skin incision the knot grasped and ch limb individually tracted until recovered from the dominal cavity This gentle steady traction on one mb at a time straightens out the spiral cone and permits thdrawal of the tubing This simple office technique for removal of the stents replaces the formidable burden a second operation to remove devices

DISCUSSION

he proper work up of the infertile couple has been ported previously (7) An essential feature of the sic study is fiberoptic laparoscopy after gamete formation in male and female reception deposition of gamete nidation and transport factors have been evaluated So valuable is the information provided at laparoscopy that only in the most unusual circumstance is one justified in attempting tuboplastv without prior laparoscopy In the primary infertility survey for a couple more simple techniques for estimating tubal patency and tubal configuration may be employed initially These include hydrotubation followed by carbon dioxide insufflation (1) which must be carried out several times if an obstructive pattern is to be entertained Also the volume of fluid introduced must exceed the routine ten ml if the presence of a hydrosalpinx with distal occlusion is to be discovered Hysterosalpingography if an entirely physiologic configuration of the oviduct is demonstrated and accompanied by a good peritoneal smear bilaterally may be accepted in the initial survey and management of a couple Since the incidence of adverse tubal factors is at least thirty five to forty per cent and since hysterosalpingography is deficient or in error at least twenty five to thirty percent of the time (6) and laparoscopy has proven therapeutic in at least twenty percent of cases with partial tubal fimbrial occlusion its use is warranted In the large number of couples referred to the infertility specialist s office who have had previous infertility studies performed and have failed to conceive despite active supervision over six months laparoscopy is mandated an essential feature of the basic study and management

able III *Time interval between tuboplasty and pregnancy*

	No	1–?	3–6	7–10	11–18	19–?6
Midportion						
Reanastomosis of previous ligation	3		1			
Anastomosis of occlusion						
Cornual implantation			?			
Fimbria	12		2	6	3	1
Bilaterally homogeneous	45	1	5	12	18	9
Bilaterally mixed	15		1	4	8	2

A specific finding at laparoscopy not achieved by any other mode of investigation is the demonstration of narrowed abdominal ostia of the oviducts referred to as phimosis On tubal perfusion

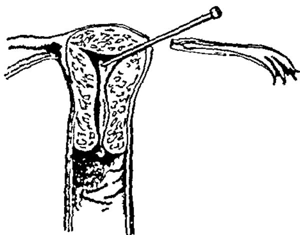


Fig 2 Opening at cornua made with a narrow trocar and cannula

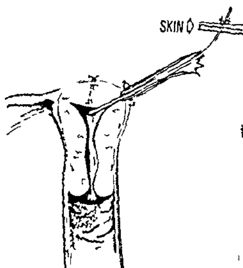


Fig 4 Interrupted sutures (4-0 chromic) used to approximate the serosa between the cornua and proximal portion of tube

under direct laparoscopic observation sacculation of the isthmic portion of the oviduct occurs and the perfused blue dye is prominently visualized through the serosal coat This observation persists after the introductory pressure of the syringe for more than thirty seconds as one drop of dye escapes from the oviduct at a time Another feature of laparoscopic observation in which hysterosalpingography frequently fails is the presence of peri tubal adhesions at points along the length of the oviduct which may impede tubal motility and alter transport of the zygote Also the presence of fimbrial

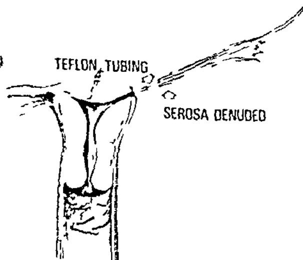


Fig 3 Teflon tubing threaded through the oviduct brought into uterine cavity with a 4-0 chromic suture and anchored to fundus

adhesions which may impair ovum pick up readi fails to alter the peritoneal smear of hysterosal pingography (Fig 6)

To define the role of laparoscopy completely i must be insisted upon that tuboplasty must not b accompanied by endoscopy at the same sit ng especially with partial tubal occlusion First th therapeutic benefit of laparoscopy is significantl high as shown in Table II The judgm nt of th role and prognosis of surgery is made hastily an under stress and not shared with the patient Final ly the combined surgical procedure imposes to long an operating time which carries the burde of added morbidity in infection and a esthen complications In our estimation only a previou inadequately described adverse laparoscopy n port warrants under unusual circumstances com bined laparoscopy tuboplasty procedure

The universal experience of a small but signif cant number of patients conceiving following hy drotubation and/or hysterosalpingography is wel established Nevertheless our experience demon strates an additional approximately twenty per cen of patients with tubal abnormalities who co ceiv after laparoscopy with no other definitive therap (Table II) This is understandable on the basis th in the anesthetized patient under direct observa tion the oviduct may be exposed saf ly to signif cantly higher pressures at tubal perfusion so th grumous material and fine synech ae may be evac

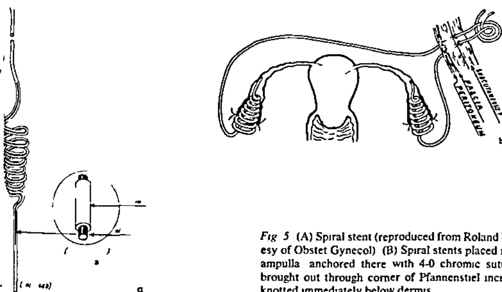


Fig 5 (A) Spiral stent (reproduced from Roland by courtesy of Obstet Gynecol) (B) Spiral stents placed into each ampulla anchored there with 4-0 chromic sutures and brought out through corner of Pfannenstiel incision and knotted immediately below dermis

d This has been observed by us on numerous casions at laparotomy for tubal plasty We usual perfuse the oviducts through either the cannula the cervical level or through the fundal area In latter we have observed the extrusion of this ft type grumous material This can be further afirmed by the microscopic examination of the pelled material

Current reports in the literature describe old and w techniques for lysis of tubo-ovarian adhesions d salpingostomy without the use of splinting de es and this in our opinion can only be deplored physiologic grounds Any manipulation that calls th a peritoneal reaction such as in dissection of hesions or electrocoagulation of adhesions will sult in the establishment of new fibrinous exudate an essential step in healing This must represent defeat for the surgical technique The subcutane s fixation of the terminal knotted portion of the ents permits intestinal motion to move the ted oviducts and inhibit formation of new fibrous adhesions and thus prevent adhesions between the distal portion of the oviduct to adjacent tructures

After laparoscopy those patients who were found to have partial tubal occlusion including those with hydrosalpinx partially occluded as demonstrated by persistent sacculations which do not disappear after thirty seconds were all followed with pre-ovulatory hydrotubation and carbon dioxide tubal insufflation described above for at least six months Most of them were followed for longer periods of time before they were recommended for tubal reconstruction As stated elsewhere only those patients who were above 30 years of age and had a history of trying to conceive for a minimum of two years without success did we in cases of complete tubal occlusion as demonstrated at laparoscopy perform tubal surgery before the trial period of six months

In cases of hydrosalpinx with distal occlusion



Fig 6 Adhesions between the fimbria and lateral wall of pelvis

we would simply incise the serosal covering and in most cases could observe a good amount of fimbria behind (as seen with 3½ times magnification of ophthalmological lenses) In this case we would suture the serosal portion backward and still insert the spiral stent and anchor it there for eight weeks Our rationale has been that by incising the serosal covering and handling the fine fimbria there usually exists the possibility to reform adhesions When left alone the opposing walls usually collapse and are in approximation with each other The insertion of the stent therefore is found to be very helpful in preventing re adhesions between its walls Prevention of the distal repaired tube from lying free and next to the abdominal contents might cause adhesions to the adjacent tissue One must remember that by suturing the serosal area backward we are exposing raw surfaces to be subjected to re adhesions The stent in place and the distal portion of the teflon anchored keeps the abdominal wall distal portion from staying in one area and thereby kept moving by the intestine

Our criteria for the spiral stent are two-fold (1) to keep the reconstructed fimbria separated and thus prevent reocclusion (2) in patients with phimosis and partial tubal occlusion after dilatation with graduated cone shaped probes the spiral stent prevents re shrinking to its original position The same holds true for the hydrosalpinx with occlusion by preventing the raw surfaces resulting from lyses of adhesions of the opposing walls to readhere Our motto is—once adhesions have been lysed a stent must be placed

Adjuvants to tuboplasty require evaluation at the same time The role of corticoids and promethazine (Phenergan Wyeth Lab) in inhibiting the formation of adhesions is not yet established (7) In pursuit of this information we are employing corticoids and promethazine in alternate cases We are convinced that the prophylactic use of antibiotics is warranted in all cases of tuboplasty since an infectious factor in the etiology of tubo-ovarian adhesions can never be ruled out with certainty at the time of surgery We therefore culture the distal portion of the tube at laparotomy A further measure to eliminate the introduction of infection is the prohibition of sexual activity during the eight weeks period the stents remain in situ We have recently added 200 cc of 6% Dextran in 5% Dextrose before closing the peritoneal cavity as additional aid to prevent post operative adhesion So far it has served a purpose Oral contraceptives for eight week are provided to prohibit the contamination of the healing epithelial surfaces by the menstruum and block cilia formation in the presence of semi rigid splinting material which might damage these functionally vital cellular elements

Additional observations gathered from our yea of experience with tuboplasty permit other pert nent conclusions to be drawn And careful analys of individual cases imparts to us a sense of a and humility toward the work we do In our ser there were three cases that met with major com plications characterized by intestinal obstru tion peritonitis and severe infection Study onstrated there were features common to th three cases All had severe pelvic endometriosis a the primary diagnosis Two of these had previo surgery for pelvic endometriosis and had po operative courses characterized by febrile episod of clinical significance The third an early cas presented marked pelvic endometriosis re ne extensive dissection following which tuboplas was performed with spiral teflon stents to prote the *fimbria from re involvement* with adhesi All three cases required laparotomy for intestin obstruction and bowel re section Most remarka was the conclusion to the third case operated f tuboplasty for the first time She conceived w h a year and delivered a full term baby Two cave may be drawn from these cases The presence severe pelvic endometriosis presents a formidab problem the surgical management of which pr disposes the patient to a stormy post-operati course frequently with super imposed infectio This combination of complications should preclu successful reconstructive tubal surgery That ev these complications may be overcome in the futu as we acquire more experience and knowledge as indicated by the third case which terminated in successful pregnancy

An additional caveat derives from experien with micro-surgical techniques We employ op thalmological lenses providing three and one h times magnification and affording adequate v ualization of all anatomic features especially the fimbriae are kept moist with saline Unl the fimbriae are kept moist with saline Until neurosurgery the employment of microsurgic techniques unnecessarily prolongs the surgi procedure and anesthesia time which may pr dispose to increased morbidity We did not fi more advantage in the rise to higher magnificatio

ble IV *Proposed classification for reporting -d up and management of reconstructive tubal gery*

ts to be accepted for classification
All other factors in reproduction have been demonstrated normal in both members of a couple
The identical operation is performed in both tubes or the status and management of the separately handled tubes are individually documented and described
of the followin data are reported
Patient s prior obstetrical history and report of all infertility studies
Tubal deficit defined at endoscopy and peak pressures applied on tubal perfusion
eration performed
Site Fimbria mid portion cornual procedure sutures used
Findings at tubal perfusion
Type of stents used duration of placement
Operative diagnosis pathological diagnosis of any resected tissue
operat ve management
Hydrotubation
Insufflation
Adjunctive medication
ural technique
postoperative performance
Patency
Obstetrical performance
a Abortions
b Live births
Ectopic and location

in three and one half times with opthalmological kes

SUMMARY

believe these results reflect a statistically significant improvement in the results of tubal reconstructive surgery The more judicious selection of patients fo tuboplasty by laparoscopy has significantly improved the prognosis for patients to whom off r surgical tubal reconstruction It is important to observ in Table I the 39 patients in whom the lex pathological findings demonstrated tuboplasty was contraindicated It must also be recognized that some of the conditions that interdicted surgery might not have been recognized on hysterosalpingography Also it is reported that hysterosalpingography missed pathology in 30% of the cases Therefore it may be said laparoscopy has permitted us to find additional cases to benefit from tuboplasty over that number suggested by hysterosalpingography These observations support our view that hysterosalpingography must not interdict early laparoscopic examination regardless of the findings Further the therapeutic benefit of laparoscopy in a significant number of patients precludes the combining of the two procedures laparoscopy and tuboplasty in most instances Table I reveals 118 patients conceived following laparoscopy

Table II reports the improved results afforded by the critical features of our technique particularly the employment of the Roland spiral stent in fimbrioplasty and splinting all anastomotic sites

These tables reflect an improvement in oviductal patency rate from 56% to 90% when patients were more discriminately selected by laparoscopy and splinting with stents was employed routinely The improved patency rate was accompanied by a concomitant rise in the pregnancy incidence to 39% of patients with sustained tubal patency

The abortion rate is 3 4% In groups the size of those reported here these figures fail to demonstrate a predilection by site of tubal repair

Table V *Classification of tubal disease*

	Right	Left	Bilateral
I Endometriosis			
A Ovary			
B Fimbria			
C Ampulla			
D Mid portion			
E Cornual			
F Cul-de sac			
II *Malformation (occlusion)*			
A Fimbrial			
1 Complete			
2 Partial			
3 With serosa only			
B Ampulla			
1 Hydrosalpinx			
2 Sacculation with dye *only*			
C Mid tube			
Complete occlusion			
D Cornual			
1 Complete occlusion			
2. Partial occlusion			
III *Adhesions*			
A Peri tubal			
B Tube–lateral wall			
C Ovary–tube			

Table VI *Classification of tubal surgery*
Previous surgery Salpingectomy Oophorectomy
Salp Ooph

	Right	Left
I *Peritoneal*		
Excision of endometriosis		
A Ovary		
B Fimbria		
C Ampulla		
D Mid portion		
II *Malformation (fimbrial)*		
A Fimbrioplasty		
B Incision of serosa		
C Dilatation of phimosis		
D Insertion of stents		
type of stent hood spiral none		
III *Mid portion occlusion*		
A Excision of occluded portion		
B Anastomosis (end to-end)		
C Stent used (teflon poly)		
IV *Peritubal adhesions* Lysis (sharp or cauter)		
Kinks removed		
V *Cornual implantation*		
A Excision of occluded portion		
B Implantation (method)		
C Stent used (teflon poly)		
VI *Adnexal adhesions* Lysis		
A Between ovary-tube		
B Tube-lateral wall		
C Ovary-omentum		
D Omentum-tube		
E Cul-de sac (type-omentum endometriosis)		
F Endometriosis		

We have only one ectopic pregnancy to report so that no conclusions may be drawn in this regard

Finally of the 1075 laparoscopies 376 were found to have tubal pathology The findings in 39 cases interdicted corrective surgery 337 were amenable to reconstructive surgery However 118 conceived after laparoscopy 14 refused surgery Therefore 205 patients had tuboplasty 90% of these had sustained tubal patency 68 had full term pregnancies 7 had early abortions and may yet conceive and carry to term

The implementation of finding tubal pathology with laparoscopy and the guidance it has provided in selecting cases for tuboplasty properly has been accompanied by additional improvement in our success with tuboplasty by the employment of routine splints in particular the introduction of the spiral teflon stent

Further improvement we believe rests upon the adoption of uniform simple classification of tubal operations so that statistically significant data can be accumulated This will permit recognition of the differences in the success rate met by the various techniques employed for tuboplasty A meaningful system of classification should include a very limited number of subsets of procedures so that sufficient data for analysis will quickly accumulate We would like to suggest the following criteria for such classification (Tables IV V and VI)

Beyond the benefits to accrue from our analysis of our current techniques for oviductal reconstructive surgery further progress will be achieved when our knowledge of tubal function on a molecular level is increased The role of hormonal activity in oviductal function in transport of gametes and zygotes is information which is being accrued Functional sphincters and their hormonal control may be altered or restored by tubal plastic surgery Tuboplasty and its adjuvants must preserve epithelial nutrition the ciliary elements and the contractile motility of the oviduct so that sperm capacitation and timely ovum transport are insured These molecular events must be better understood

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THE LATZKO OPERATION FOR VESICO VAGINAL FISTULAE

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o-vaginal fistulae are seen infrequently in de ed countries the main causes of operable ae being injuries due to hysterectomy radical rectomy or radiotherapy for carcinomas of erix The operative approach depends on factors such as the size and localization of the t aetiology of the fistula presence or absence ier lesions in the lower urinary tract or bowel techniques and approaches have been pro-] For the uncomplicated vesico-vaginal fistula pproach preferred by gynecologists is the vagi ne either the Fueth operation in German ing countries or the SIMS procedure in the sh speaking world A good alternative espe in the posthysterectomy fistula but also in fistulae is the Latzko procedure

tzko (8) described this operation in 1913 and its high occlusion of the vagina He had used it essfully in 3 cases 1 with a recto-vaginal and 2 vesico-vaginal fistulae Independently Wert is said to have used the same method Later pera ion seems to have been almost forgotten Falk (4) rediscovered it

e Latzko procedure has definite advantages the Sims or the Fueth operation in cases of ly situated relatively inaccessible fistulae se advantages are (12) a high success rate rical ease little shortening of the vagina

e Latzko procedure may also be performed for ller radiation fistulae In these cases the col isis has to be more extensive

MATERIAL AND METHODS

e last 22 years 1953–July 1976 we have operated on tients with vesico-vaginal fistulae 61 uncomplicated 4 complica ed (combined with other defects of the ary and/or intestinal tract) Most of these cases were red from other institutions In the complicated cases various techniques—often a combined abdomino-vaginal approach—were chosen with or without the interposition of healthy tissue such as gracilis muscle (Ingelman Sundberg 6) bulbo cavernosus patch (Martius 10) or peritoneum (Hohenfellner et al 5) Of the uncomplicated 61 fistulae 23 were operated according to the Fueth or the Sims and 38 to the Latzko technique

Time of operation It is generally accepted to postpone the operation for 6 or even 12 weeks and longer (? 4 7 10 13 14) after the occurrence of a fistula and to wait 6 months or longer in cases of a radiation induced defect If surgery is attempted earlier than 6 weeks the results are less favorable (1) During this interval a small postopera tive fistula may close spontaneously under proper treat ment More important than the time factor is that any local irritation or bladder infection should be cleared before surgery is attempted

The preoperative treatment is directed against local and bladder infection Estrogens may promote healing in postmenopausal women To exclude other lesions of the urinary tract a cystoscopy and an i v pyelogram or an isotope renogram should be made

Technique The basic principle underlying the Latzko procedure is the observation that normally the vagina is collapsed the anterior wall lying on the posterior wall A posthysterectomy vesico-vaginal fistula is always situated in the anterior wall If the area surrounding the fistula is de-epithelialised the corresponding raw surfaces of the two walls may be approximated without any tension It is important to remove only the thin epithelial layer and not the underlying connective tissue Apart from the fact that the wound may always be closed without tension Latz ko s technique has three additional advantages (12) there is no danger of an ureteral damage during surgery even a temporary postoperative overdistension of the bladder does not endanger the results the repair is generally suc cessful even after previous unsuccessful attempts

If access is difficult the operation may be facilitated by making a median or mediolateral episiotomy and/or by pulling the fistula downwards with stay sutures Allis clamps or a Foley catheter (Fig 1) introduced into the fistula If the defect is large enough the catheter may be introduced directly through the vagina into the bladder If this is not possible a probe is passed through the urethra and through the fistula A catheter is then fixed to the tip of the probe By withdrawing the probe the catheter is pulled into the bladder After filling the balloon the opera

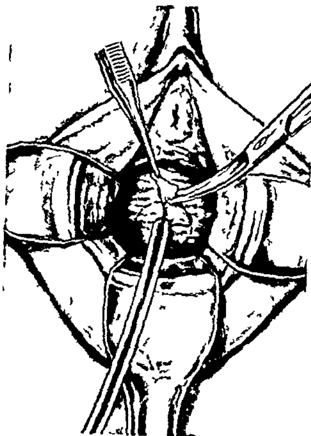


Fig 1 For explanation see text (Käser in Matouschek & Kiermeier ref 11)



Fig 2 For explanation see text (Käser in Matouschek & Kiermeier ref 11)

tive field may be pulled *towards* the introitus of the vagi na

The fistula is now *circumcized* at a distance of 1 to 1 5 cm on the anterior and 1 5 to 2 cm on the posterior wall (Fig 1) The posterior *dissection* has to be more extensive because this wall has to *cover the fistula* In order to facilitate the *operation* the circumcized area may be subdivided in 4 *quadrants* which are dissected successively

‹ important to *remove all* epithelium from the circum area to the edge *of the fistula* opening Generally ‹ is little *bleeding* and no hemostasis except hot saline packing is necessary *An* occasional bleeding vessel may be coagulated cautiously

The wound is now closed in one or two layers with 4 to 5 interrupted *sutures* according to the size of the fistula and that of the *vaginal* fornix using atraumatic needles and absorbable sutures 3-0 to 4-0 (Fig 2) More stitches ar unnecessary and possibly harmful because of devitalisa tion The vaginal mucosa is then closed either with a fe fine absorbable or non absorbable stitches The latter ar removed after some weeks The bladder is drained for 7 6 10 days via the urethral and/or suprapubic route Late we have been using the suprapubic method routinely be cause it is more comfortable for the patient and probabl allows earlier resumption of spontaneous micturition

Table I *Vesico-vaginal fistulae (Latzko operation)*

1st operation successful	35
2nd operation successful	2
3rd operation (combined abdomino-vaginal successful (radiological fistula)	1
Total	38





Fig 3 Schematic representation of the approxima on of the bladder mucosa and the two layer closures (Käser in Matouschek & Kiermeier *Ref 11*)

3 is a schematic representation of the different

ays 6 to 8 the catheter is clamped daily for a of 2 hours and removed on days 7 to 10 if the is able to empty her bladder Micturition general ents remarkably little difficulty after suprapubic e

treatment Early ambulation presents no difficul treatment consists of antibacterial drugs large es of fluid daily bladder irrigation supervision of drainage and estrogens in postmenopausal pa

patient may leave the hospital after 9 to 10 days or if she so desires She should be instructed how t to have intercourse before 8 to 10 weeks have . Early intercourse has been the cause of failure in ublished cases

RESULTS

38 fistulae 9 occurred after operative and/or on treatment for carcinoma of the cervix and er hysterectomy—abdominal or vaginal—or on of the cervical stump In all but 3 cases the peration resulted in cure In two cases a sec peration was necessary and in 1 case only the approach was successful In many cases one cases even two unsuccessful attempts at g the fistula by various techniques had been before we saw the patient The size of the e varied from a barely visible pinpoint defect of 2 to 3 cm in diameter (Table I)

ere are a few reports concerning the Latzko tion in the literature with equally good results 7 9 12) According to a paper from Graz ria) and Erlangen (Germany) 29 out of 31 ae were cured by the Latzko operation (12) patients had to be reoperated

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INVERSION OF THE APPENDIX

There is nothing new under the sun

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naecologists are trained to operate in the female elvis and their expertise is in those organs of the bdomen lying below the umbilicus They should ave learned in their years of training to recognise ll the common variations from the normal in the eritoneal cavity Diagnosis is the awareness of a ondition seeking and finding it

This is not to say that gynaecologists should perate beyond their recognised realm which is the emale genital tract only to emphasise that it is the luty of anyone opening the abdomen to examine by ye and by the hand all the organs available for ex ploration and to note and make available for others nformation about abnormalities which may be found in the kidneys gall bladder liver and spleen For instance the presence or absence of Meckels diverticulum should be recorded in the operation notes

Th vermiform appendix is the extra genital organ which most commonly intrudes into the gy ae ologist's territory and it is tempting to remove it by appendicectomy (appendectomy) which in l es cutting the base of the appendix from its continuity with the caecum exposing the peritoneal cavity to the bacterial flora of the intestinal tract and burying the stump In searching for a safer way of dispo ing of this useless and potentially danger o s organ one realised after some years of thought that here was an organ the blood supply of which could be divided easily and the whole appendage turned in-side-out where it would necrose and fall o t saf ly into its parent organ the caecum

A search of the literature showed that George M Edebohls read a paper about this procedure before the Medical Society of the State of New York on February 5th 1895 Doctor Edebohls gives a full and reasoned account of the procedure and states in view of the apparent simplicity of the concep tion however he should not be greatly surprised to learn that he had but furnished an additional illustration of the truth of the adage nothing new under the sun

He goes on to say— the term inversion of the appendix sufficiently explains itself It consists in inverting into the lumen of the large intestine either the entire appendix or any part thereof remaining to the caput coli so that the appendix or what re mains of it instead of being free in the peritoneal cavity is now free within the lumen of the bowel The mucous lining of the appendix thus inverted becomes the external coat and its former serous covering lines the new lumen along the whole ex tent of which it lies in contact with itself The mouth of the inverted appendix on the peritoneal aspect of the caput coli is closed by suture to prevent re inversion of the inverted appendix

Inversion of the appendix should not be attempt ed in the case of acute appendicitis because oedema of the appendix wall reduces mobility Another contra indication is narrowing of the lumen of the appendix in the proximal portions for it must be emphasized that for successful inversion the most distal part must be able to pass *within* the proximal part of the appendix

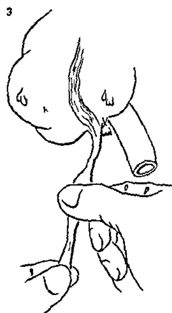
When demonstrating or describing this procedure the inevitable question is asked what happens to the inverted appendix? When the main blood supply has been divided the appendix is cast off and passes into the colon if the division of the blood supply has been incomplete the appendix may not slough however it will not cause an acute crisis because the mucous surface is outward facing and inflammation does not occur within a confined space

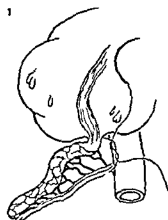
It is most important that the patient and her family doctor know what has happened to the appendix They cannot be told that an appendicectomy (appendectomy) has been carried out The most easily understood explanation is that the blood supply has been divided and the appendix turned inside out as when the finger of a glove is pushed into the palmar space

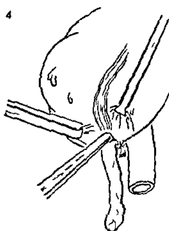
The stages of the procedure for inversion of the appendix are best described by the following drawings

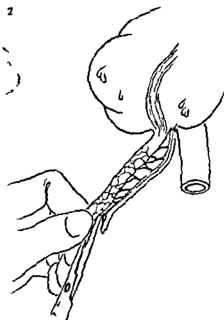
1 A ligature has been passed to ligate the appendicular artery at the base of the appendix

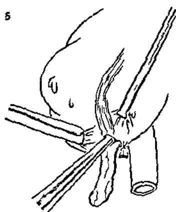
2 The meso-appendix is divided as closely as possible to the appendix

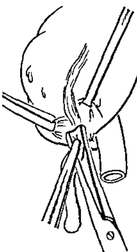












3 All the contents of the appendix such as faecoliths are pushed from the distal end into the caecum

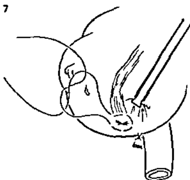
4 The muscle wall of the caecum is picked up with tissue forceps and the base of the appendix inverted with Spencer Wells forceps or non tooth dissecting forceps

5 The continuation of (4)

6 If there is difficulty in pushing the appendix into the caecum the opening may be widened with blunt sinus forceps

7 The appendix has been inverted into the caecum and the peritoneal mouth is closed by a purse string suture of chromic catgut no 00 and a further purse string suture inserted to bury the first

7



ACKNOWLEDGEMENT

This non scientific and not original contribution is submitted as a practical reminder that there is nothing new under the sun And in grateful thanks to Axel Ingelman Sundberg for his friendship and stimulating thoughts when we have met in many parts of the world

I wish to thank Miss Patricia Archer Medical Illustrator at Guy s Hospital London England and her staff for the drawings

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IS THERE A CHANGING EPIDEMIOLOGY OF PREMALIGNANT LESIONS OF THE CERVIX?

Results of Cytologic Screening of Pregnant Women

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stract The selection of women approached for ...ologic screening is based on previous studies on age ...tribution and prevalence and consequent considera ...ns on the risk of developing invasive carcinoma In ...der to check if this is appropriate the results of the ...reening of pregnant women being selected irrespective ...their age has been studied for two periods 1961–64 and ...7 The frequency of lesions was remarkably high ...ong the teenagers of both periods A significant in ...ase in the incidence of lesions was noted for the period ...7 This increase is most evident in the ages 21 to 30 A ...ft to more severe lesions was found among the teen ...ers and in the groups between 31 and 40 In conclusion ...re effort should be made with respect to cytologic ...reening of young women particularly when pregnant ...e increased frequency of cytologic atypias among wom ...between 21 and 30 should focus the attention to the ...ssibility that the epidemiology or premalignant lesions ...the uterine cervix is changing

...he basis for screening of premalignant lesions of ...e cervix is found in studies on the prevalence and ...cidence of the lesion in different age groups and ...her groups of the population considered at high ...sk. The interest and financial engagement of the ...ciety in screening programs differs considerably ... different countries even in different parts of the ...untry as is the case in Sweden Here the ages ...om 30 to 50 are in focus being checked every ...ach year In addition pregnant women are being ...reened at the maternity welfare centers since the ...rly sixties irrespective of the age of the woman ...e screening programs cover only part of the tar... ...population Beyond comparison the best cover... ...e is obtained within the maternity welfare system ...hich serves a very high percentage of the pregnant ...omen

There is need for a reevaluation of the Swedish screening programs and if necessary to define new recommendations for the next decade preferably uniform for the entire population of Sweden The basis for the present screening programs was established several years ago and may have become inappropriate for two reasons First the interval between the cytological samplings may be too long (8) second the age groups at risk may have changed because of alterations in epidemiology The second probability cannot be checked by study of attendants to the current screening programs or by study of the age distribution of premalignant lesions as figures obtained in this way are based on selected age groups where women below 30 years of age are not represented to the same degree The screening organization of pregnant women in Swe den instead has not taken into account the age of the woman and may therefore be used to check if there is reason to remodel the general screening program because of a changing epidemiology of the cervical lesions

The present study compares two equally sized groups of pregnant women from around 1962 and 1972 with respect both to the relationship of inci dence to age and to the distribution of various de grees of dysplasia and cancer in situ The aim was to study if the frequency of premalignant lesions had changed in these groups of women during a ten year interval

MATERIAL AND METHODS

A total of 4 788 vaginal smears taken from attendants to the maternity welfare centers in the Stockholm area form

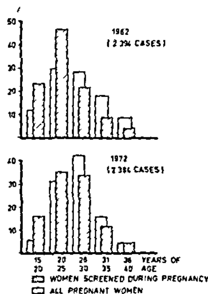


Fig 1 Relative age distribution of screened and all pregnant women in Stockholm

the basis of the study 2394 consecutive vaginal smears from the period October 1961—September 1964 and 2384 from 1972 were studied The interval between the two groups is thus approximately 10 years and the first period will in the following be briefly referred to as 1962 The age distribution in the two groups is shown in Fig 1 Here the age distribution of the mothers taken from the birth statistics of the corresponding population is also shown The figure shows for both periods an overrepresentation of smears taken from young pregnant women and an underrepresentation among the older women In addition more smears were taken from young women in the earlier period This may be due to neglectance of taking smears from women who recently had a smear taken for some other reason There is reason to assume that such a neglectance was more frequent in the earlier period which would explain why a longer period was required in the early sixties than later to obtain the same number of smears This dissimilarity of the two groups will be considered further in the discussion

The cytologic slides were stained according to Papanicolaou and primarily examined by cytotechnologists The cytologic findings were allotted to either of five diagnostic groups using the classification of Papanicolaou All slides considered to contain cells of possibly premalignant or malignant significance were reviewed by cytopathologists being responsible for the final diagnosis which includes a verbal statement In our screening routine usually a Pap III is equivalent to moderate dysplasia Pap IV related to severe dysplasia or carcinoma in situ and Pap V implies a strong suspicion of invasive carcinoma

To allow comparisons between materials collected several years apart the diagnostic criteria must have been practiced similarly during the two periods under study This was tested by reviewing 190 consecutive positive smears from 1962 and 195 from 1972 The initial classifica-

Table I *Revision of cytologic preparations fro 1962 and 1972 by four different senior cytotechnologists*

Cyto-technologist	Year	Papanicolaou Same (%)	Higher (%)	Lower (%)
A	1962	67	9	24
	1972	64	16	20
B	1962	46	33	21
	1972	69	16	15
C	1962	57	28	15
	1972	68	18	14
D	1962	61	18	[illegible]
	1972	54	19	27
Average	1962	57	27	[illegible]
	1972	64	17	19

tion of these cases is given in Fig 2 It is evident that material from 1962 shows a slight excess of more advanced changes as compared with that from 1972 A few cases in Pap I were included because of incorrect initial filing which explains their presence in the group of positive cases All these smears were now independently reviewed by four senior cytotechnologists

This revision showed that there was no apparent difference between the evaluations of 196 and 1972 (Table I) The same result was reached in 60 5% In most cases differences in evaluation were restricted to one Pap group i e a slide primarily allotted to e g group III was at revision in 97% of the cases allotted to either group II III or IV Thus the criteria for the cytologic diagnosis have been practiced in the same way during the two periods studied

RESULTS

Among the smears from the first period (1961-64) abnormal cytology was recorded in 135 specimens (5 6%) in contrast to 170 (7 1%) in the material from 1972 (Table II) This difference is statistically

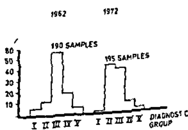


Fig 2 Relative distribution with respect to diagnostic groups (Pap) of consecutive positive smears from 1962 and 1972

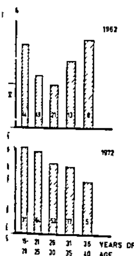


Fig 3 Frequency of all squamous cell abnormalities (Pap II–IV) in maternity welfare patients from 1962 and 1972 The absolute numbers are shown inside the respective columns

...nificant (χ^2=4 ?0? p<0 05) The cytologic ...nges vary from mild dysplasia to carcinoma in situ. No case of invasive carcinoma was detected The age distribution of all cytologic changes is shown in Fig 3 were the difference between the two materials is notable although the youngest group shows a high incidence at the same level in both In the age group 21–25 the difference is statistically significant (χ^2=5 742 p<0 02) and also in the age group 26–30 (χ^2=4 444 p<0 05) with a higher incidence in the material from 1972 In the other age groups the differences are not statistically significant If only the more significant atypias (Pap III and IV) are considered the difference between the two periods is similar (Fig 4)

In addition the relative distribution of the different grades of cytologic atypia (dysplasia) have changed during the period studied The proportion

Table II *Squamous cell abnormalities in maternal welfare patients 1962–1964 and 1972*

	No of screened women	Women with squamous cell abnormalities	
		Number	Frequency (%)
[1962–64]	2 394	135	5 6
[1972]	2 384	170	7 1
Total	4 778	305	

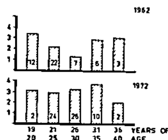


Fig 4 Frequency of more severe squamous cell abnormalities (Pap III and IV) in maternity welfare patients 1962 and 1972 The absolute numbers are shown inside the respective columns

of Pap III and IV of all atypias has increased particularly among teen agers and in the group between 31 and 40 years of age (Fig 5) As only 4 cases with Pap IV were found 1962 and 5 in 1972 no conclusion can be drawn about the incidence of those cytologic atypias which indicate carcinoma in situ

DISCUSSION

The problem of rational and economically acceptable screening of the population with respect to diseases of humanitarian and socio-economic significance has long been a main interest for governmental and other institutions concerned in the welfare of the population The benefit of such screening programs to detect early cervical neoplasia has been demonstrated e g in British Columbia (1) Kentucky USA (2) and Østfold Norway (6) In Sweden a distinct reduction of the incidence of cancer of the cervic has been reported in those counties where screening programs were first initiated (5) For the whole country a moderate reduction of the incidence of cancer of the cervix has recently been reported (11)

The reported effect of the Swedish screening for

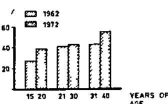


Fig 5 Proportion more severe squamous cell abnormalities (Pap III and IV) of all abnormalities (Pap II–IV)

cervical neoplasias is only moderate which may be due to inappropriate attention to the age groups at risk Different sociological conditions are well known to influence the risk of developing carcinoma of the cervix A reevaluation of the groups of the population being approached for screening may be necessary as these conditions may be changing

The present material indicates that during the first period (1961–64) more women were examined cytologically because of clinical symptoms or findings or because of no recent cytologic examination This would be expected to give a higher figure of the incidence of positive findings than is actually present in the age group in question In spite of these circumstances the frequency of positive findings found is lower in the 1962 material than in the material from 1972 The real difference in this respect between the two groups must thus be still higher than indicated by the present figures

Moreover considering the severity of the lesions discovered a change to more severe lesions is indicated by the obtained results (Figs 4 and 5) although the incidence of carcinoma in situ shows no change and no invasive cancers were found among our cases As the clinical significance of mild cytologic atypias classified as Pap II may be limited it is noteworthy that the differences between the two groups persist even when those cases presenting mild atypias are excluded (Figs 4 and 5) In this context it should be pointed out that cytologic screening during pregnancy is equally reliable for early cancer detection as in the non pregnant state (7 10) It is therefore generally recommended that pregnant women should be screened by means of exfoliative cytology for the purpose of cancer detection

During the past ten years a considerable increase in the number of cases of carcinoma in situ reported to the Swedish cancer register has been a matter of concern (3) The increasing incidence among younger women may of course not represent a true change in the age distribution of the lesion but may be caused by increasing screening activities in the younger ages combined with a successive removal by treatment of asymptomatic cases in the upper age groups thanks to the screening program itself Anyway the recent figures of the age distribution of carcinoma in situ have been taken as an indication that an extension of the program to younger age groups is recommendable This was also emphasized by Wallace & Slankard (9) who found carcinoma in situ in 12 of 7520 teenagers screene (0 16%)

However the number of cases of carcinoma i situ reported in Sweden exceeds the number of invasive cancers by a factor of five at presen which was not the case a couple of years ago A change in the practice of the diagnostic criteria ma therefore be suspected which should lead to a fals high number of diagnoses These statistics ar based upon the results of histopathological nation of surgical specimens however Our preset study is based on examination of cytologic smear only Revision of a number of slides from 1962 an 1972 excludes a change of opinion at our laborator with respect to the diagnostic criteria (Table I There is therefore good reason to consid r the n creased incidence of cytologic changes of possN premalignant significance as true

In the two clinical materials reported here the c a remarkably high incidence of cytologic change among the teen agers As teen agers constit group where previous cytologic examinations a not common this figure may be higher than th actual incidence in the age groups in questio Furthermore the group of teen agers reported h may not be representative for all teen agers pregnancy in this age group may indicate a high sexual activity and an earlier sexual debut possib combined with a lower standard of contraceptio This might also indicate lower socioeco omic a hygienic standards of living and perhaps also higher degree of promiscuity which all are facto known to increase the risk of cervical neoplasia.

The incidence of cytologic abnormalities (Pa III–IV) among the pregnant teen agers of o r stu (in total 11 out of 621 or 1 8%) should be compar with the much lower incidence—0 17%—amo non selected teen agers in Chicago recently r ported by Fields et al (4)

Irrespective of the reason the observed high fr quency of lesions among young pregnant wome the present material defines them as a group increased risk and strongly indicates that th should be included in cytologic screening program The high frequency of carcinoma in situ amo The high frequency of carcinoma in situ amo teen agers reported from Kansas City was given th same inference (9) In addition both the increas frequency and severity of the lesions during t period studied indicates the n cessity of expa du the general screening programs to younger wome

that has been customary until now. The results also indicate the importance of repeating retrospective studies of this kind at regular intervals in order to detect future changes in the epidemiology of early cervical neoplasia.

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EFFECT OF ALKOXYGLYCEROLS ON THE FREQUENCY OF INJURIES FOLLOWING RADIATION THERAPY FOR CARCINOMA OF THE UTERINE CERVIX

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Abstract The incidence of injuries following intracavitary and external radiation therapy is markedly decreased in all stages of the disease by the administration of alkoxyglycerols Complex injuries (due to radiation injury and tumour growth in combination) were reduced to about 1/3 in a group receiving alkoxyglycerols prophylactically i e before during and after radiation treatment when compared with a control group Using non prophylactic administration of alkoxyglycerols i e during and after radiation treatment no effect was observed on complex injuries while—as for the prophylactic group—the injuries due to radiation only were significantly decreased The use of so called increased amount of radium in the intracavitary irradiator was followed by an unexpectedly high incidence of radiation injuries which was considerably reduced however by alkoxyglycerols especially when administered prophylactically

Alkoxyglycerols are found in small quantities in several natural products They are relatively abundant in the haemopoietic organs of mammals particularly the bone marrow These substances also occur in relatively high concentrations in the human mother s milk They occur most abundantly however in the liver oil of certain species of shark These oils contain up to 50% of alkoxyglycerol esters (1 7 8) The general formula for alkoxyglycerols is CH_2OH CHOH CH_2O R where R is a long-chain aliphatic radical

The alkoxyglycerols have earlier proved to be of medical interest The first studies commenced with the oral administration of different fractions of calf bone marrow to cases of leukemia in children Alkoxyglycerols promote the growth of Lactobacillus lactis (1) and the formation of antibodies (2 4) and to some extent they prevent leucopenia and thrombocytopenia as a result of radiation The administration of alkoxyglycerols before during and after radiotherapy for carcinoma of the uterine cervix also brings about higher survival rates than if radiation treatment alone is given (1 2)

The aim with the present study has been to investigate whether or not alkoxyglycerols administered in a prophylactic or non prophylactic manner influence the incidence of radiation injuries and the growth of residual or recurrent tumour following radiotherapy for carcinoma of the uterine cervix Problems connected with the development of radiation tissue damage following radiotherapy have earlier been elucidated in several publications from the Radiumhemmet in Stockholm where all patients included in the present study received their treatment (6 9 10 11 12 13 14)

MATERIALS AND METHODS

The clinical experiments in this study have been conducted using alkoxyglycerol preparations from the liver oil of the Greenland shark The preparation produced by AB Astra with the working name AT 18 is a concentrate containing 85% free alkoxyglycerols The content of different alkoxyglycerols from various sources is given in Table I

The alkoxyglycerols were administered orally in capsules 2 capsules 3 times a day each capsule containing 0 1 g of alkoxyglycerols The total daily dosage thus was 0 6 g

The series of cases with invasive carcinoma of the uterine cervix treated at the Department of Gynecology Radiumhemmet Stockholm were reviewed during various periods The patients comprised all stages see Table II and were allotted to one of the following groups

Table I *The percentage composition (weight) of alkoxyglycerols from various sources*

Analyses according to Hallgren and Larsson (2 3) The number of carbon atoms in the first column refers to the long chain component of the molecule The number after the colon denotes the number of double bonds

Alkoxy glycerols	Human bone marrow	Human milk	Liver oil Greenland shark
14 0			2 0
15[a]			0 7
16 0	29 4	23 9	9 1
16 1		trace	10 8
17	7 6	3 6	3 6
18 0	24 6	22 8	2 8
18 1	16 7	33 8	59 4
18 2		1 4	1 6
18 3			?
19[a]	6 1	2 4	1 5
20 0	2 9	1 6	
20 1	3 2	2 3	6 2
22 0	0 7	0 7	
22 1	5 1	3 4	2 2
24		2 1	

Both branched and normal chains C_{15} C_{17} and C_{19} are present

I Patients given alkoxyglycerols prophylactically i e during 7 days before during the treatment period and for 1–3 months after the completement of therapy

II Patients given alkoxyglycerols only during the period of radiotherapy and for 1–3 months thereafter non prophylactic" administration

III Patients given radiotherapy only

Groups I and II cases were treated during the period January 1 1964 – February 15 1966 During this period 99% of the patients with carcinoma of the uterine cervix received alkoxyglycerols Group III patients were treated during 1963 (348 patients) and February 16 – December 31 1966 (309 patients)

In addition to the patients followed up for more than five years and characterized above a double blind study comprising 279 patients was conducted 1970–1972 These patients have been followed up for 3 5 years from the initiation of therapy

The treatment was in almost all cases initiated with intracavitary radium application This consisted typically of two radium insertions separated by an interval of about three weeks 53–200 mg of radium was homogeneously distributed in an interauterine applicator 19–70 mm in active length The enclosure was 0 30 mm Au + 0 35 mm Pt and a stainless steel container with a wall thickness of 2 00–2 75 mm In cases in which both intrauterine and intravaginal radium was applied no radium was introduced in the distal 15 mm of the cervix whereas in cases of endocervical tumour growth as well as in cases in which the growth had extended paracervically the amount of radium in the intrauterine irradiator was increased (increased amount of radium) and radium sources were applied also in the low endocervix No radium was inserted in the vagina The vaginal radiu when employed was enclosed in a flat or curved a plicator or in a few cases in two cylinders so maximum surface area and it was pl ced as close to th tumour as possible The applicators were held in pl a tampon which also increased the distance to the rectu 58–250 mg of radium were used in the vagina

The computation of doses delivered to the posteri wall of the bladder and to the anterior wall of the rectu was made on the bases of routinely performed dose ra measurements Consecutive dose rate values were note at centimeter intervals progressing from the bladder ba caudally through the urethra and along the rectal wa Measurements were in all instantaneously performed w a slightly modified Siemens Gammameter with the patie in lithotomy position immediately after the applicatio the intrauterine sources (9 10 15) The external radi therapy was given either with conventional roentgen ra or with cobalt irradiation according to one of the follow techniques

Four fields two abdominal and two gluteal we utilized when conventional roentgen rays were used I exposure of 6×400 R was given over 4–6 weeks T external irradiation using Cobalt 60 two opposed beam was administered through 250–400 cm² anterior and p terior fields An exposure of 3 000–5 000 R was given fractions of 300–400 R six days a week Lead shields we sometimes placed over the site of the uterine cervix in t anterior or the posterior beam or both i an attempt

Table II *Definitions of clinical stages*[a]

Stage I	Carcinoma strictly confined to the cervix
Stage I A	Cases of early stromal invasion (pre clinical carcinoma)
Stage I B	All other cases of stage I
Stage II A	The carcinoma extends beyond the cervix but has not extended on to the pelvic wall The carcinoma involves the vagina but not the lower third No parametrial involvement
Stage II B	Th carcinoma extends beyond the cervix but has not extended on to the pelvic wall The carcinoma involves the vagina but not the lower third Parametrial involvement
Stage III	The carcinoma has extended on to the pelvic wall On rectal examination there is no cancerfree space between the tumour and the pelvic wall The tumour involves the lower third of the vagina
Stage IV	The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum

[a] Definitions according to FIGO (International Federation of Gynecology and Obstetrics)

Table III *Injuries following radiation therapy. All stages included*

I = total injuries. R = injuries due to radiation treatment. C = complex injuries due to tumour growth or to a combination of tumour growth and radiation treatment. N_1 = number of patients with injuries. N = number of patients with complex injuries. M = more than one injury per patient: multiple injuries

Group	No of pats	I No	I %	R No	R %	C No	C %	N No	N %	N No	N %	M No	M %
1963–1966													
I	4 8	83	18 1	59	1[illegible] 9	[illegible]4	[illegible]2	79	[illegible]		4 8	5	1 1
II	381	93	24 4	34	8 9	59	15.5	69	[illegible]	41	10 8	[illegible]3	6 0
III	657	244	37 1	150	22 8	94	14.3	[illegible]	[illegible]	6	11 6	43	6.5
1970–197?													
I	137	36	26.3	28	20 4	8	5 8	3	[illegible]3	8	5 8	4	2 9
III	14	74	5[illegible] 1	40	28 2	34	23 9	5	35 6	4	16 9	16	11.3

I Administration of alkoxyglycerols *prophylactically* and during radiation treatment

II Administration of alkoxyglycerols *only* during radiation treatment

III Radiation treatment only

... those portion of the pelvis already having received a high dose of radiation from the intracavitary sources. With a three beam technique Cobalt irradiation was delivered through one 250 cm² anterior field and two ... cm² lateral field. Weekly tumour doses were 700–800 rad with the total tumour dose being 4 000–5 000 rad. A shielding block was sometimes used in the anterior beam in all or in part of the fractions. For data regarding the calculation of the dose from the external irradiation the reader is referred to previously published reports.

In the calculation of the incidence of radiation injuries (bladder, rectum, ureters and intestine) the principles given by Kottmeier (14), Kottmeier & Gray (13) and Gray & Kottmeier (6) have been used in this investigation.

In earlier follow-up studies regard has been paid to injuries due to radiation treatment only (R). In this kind of study however it has been necessary to include the injuries due to tumour growth and to the combination of radiation tissue damage and residual or recurrent tumour growth. This is because the alkoxyglycerols may have a ... target of action. These injuries due to either tumour growth or to tumour growth and radiation damage in combination are called complex injuries (C). The sum of (R + C) is defined as the total number of injuries (I). Furthermore in this study of the effects of alkoxyglycerols in connection with radiotherapy it has been considered necessary to give figures for the incidence of occurrence of more than one injury per patient, i.e. multiple injuries (M).

The injuries have been classified according to the following schedule given by Kottmeier:

Grade I. Injuries producing mild subjective symptoms accompanied by minimal objective changes in the mucosa. These injuries are considered as radiation reactions and have consequently been omitted.

Grade II. Injuries which are composed of moderately severe objective changes such as areas of necrosis, ulcers or moderate stenosis.

Grade III. Bladder and ureter injuries comprising radiation fistulas and rectal and intestinal injuries comprising stenoses that require colostomy.

Grade IV. Rectal and intestinal injuries which are all fistulas.

Injuries which appear within three months of surgery plus radiotherapy have been excluded and those injuries which are not clearly related to the radiation treatment or to tumour growth have also been omitted. Only the injuries which appear within 5 years after the onset of radiation treatment have been taken into consideration in this investigation. Patients with complex injuries (C) have clinically detectable cancer, residual cancer or recurrent tumour growth, confirmed by biopsy or autopsy.

RESULTS

Reduction of injuries after administration of alkoxyglycerols

The effect of alkoxyglycerols on the incidence of injuries following radiation treatment has been studied comparing groups I and II with each other and with the control group III: the total number of injuries, injuries due to radiation treatment and complex injuries in the different groups are given in Table III A.

It is observed that

1 The incidence of injuries is considerably lower in the alkoxyglycerol groups than in the control group—especially for group I where alkoxyglycerols have been administered prophylactically. The incidence of total injuries is reduced to about 50%.

2 Complex injuries are reduced to about 1/3 in the prophylactic group compared with the control group.

Table VII *Incidence of injuries associated with two different modalities of intracavitary treatment*

Group	No of pats	I No	I %	R No	R %	C No	C %	N_I No	N_I %	N_C No	N_C %	M No	M %	3 year survivals No	3 year survivals %	5 year survivals No	5 year survivals %
A 1963–1966																	
Intrauterine irradiator <100 mg Ra eks vaginal irradiator <90 mg Ra eks at both treatment courses (L)																	
I	224	38	17 0	29	13 0	9	4 0	36	16 1	7	3 1	2	0 9	190	84 8	176	78 6
II	178	32	18 0	14	7 9	18	10 1	23	12 9	12	6 7	8	4 5	138	77 5	130	73 0
III	349	92	26 4	58	16 6	34	9 7	70	20 1	28	8 0	17	4 9	289	82 8	274	78 5
Intrauterine irradiator >100 mg Ra eks and/or vaginal irradiator >90 mg Ra eks at one or both treatment courses (E																	
I	230	45	19 5	30	13 0	15	6 5	42	18 3	15	6 5	3	1.3	164	71 3	139	60 4
II	202	61	30 2	20	9 9	41	20 3	46	22 8	29	14 4	15	7 4	106	52 5	93	46 0
III	299	152	50 8	92	30 8	60	20 1	119	39 8	48	16 1	26	8 7	172	57 5	149	49 8
B 1970–1972																	
Intrauterine irradiator <100 mg Ra eks vaginal irradiator <90 mg Ra eks at both treatment courses (L)																	
I	106	24	22 6	18	17 0	6	5 7	22	20 8	6	5 7	2	1 9	86	81 3		
II	115	50	43 5	30	26 1	20	17 4	35	30 4	15	13 0	12	10 4	86	74 8		
Intrauterine irradiator >100 mg Ra eks and/or vaginal irradiator >90 mg Ra eks at one or both treatment courses (F																	
I	27	12	44 4	10	37 0	2	7 4	10	37 0	2	7 4	2	7 4	18	66 7		
II[b]	25	21	84 0	10	40 0	11	44 0	15	60 0	7	28 0	3	12 0	13	52 0		

Group I Prophylactic treatment [b] Group II Controls

radiation injury and residual or recurrent tumour growth The prophylactic treatment with alkoxy glycerols in combination with radiotherapy apparently prevents the development of radiation damage and the growth of the tumour separately or combined Non prophylactic administration of alkoxy glycerols does not seem to influence the tumour growth—but still protects against radiation damage

It has been worth while to include the complex injuries in this study since the incidence of these injuries is characteristic for the different groups a great reduction was seen in case of prophylactic administration with alkoxyglycerols (group I) while no reduction was observed when these compounds were given only during the radiation treatment (group II)

The complex injuries (C) are in all the studied situations reduced to about 1/3 when alkoxyglycerols are administered before during and after radiation treatment The difference between the incidences of complex injuries in group I (prophylactic group) and group III (control group) is statistically significant $p<0\ 001$ Prophylactic administration is therefore of paramount importance for the reduction of the incidence of total injuries and especially for the reduction of complex injuries The administration of alkoxyglycerols merely during and aft radiation therapy does not reduce the incidence of these injuries

In this connection it is of interest to mention th the capacity for forming antibodies after va tion can be influenced by the administration of al oxyglycerols This fact was observed in a study i which patients were vaccinated against typhus paratyphus one day before and one day after th implantation of radium In the group given alkox glycerols certain antibodies were formed to a grea er extent than in the group receiving merely radia tion treatment (4) It is therefore probable that th general immunological response can be enhance by treatment with alkoxyglycerols and thereby th defence mechanism of the body against maligna cells intensified

The introduction of the concept of complex in juries facilitates a probable explanation why th incidence of radiation injuries is higher in the pro phylactic group than in the non prophylactic group

As mentioned before no decrease of incidence complex injuries is observed when alkoxyglycerol are administered only during radiation treatm However there is a remarkable effect on the radia tion injuries which are reduced from 22 8% 1

1% if all patients are taken into consideration the decrease of radiation injuries is even slightly higher than for the prophylactic group Tables III A and VII A The suggested explanation would be that complex injuries (C) are representative of two components one $C_{R T}$ is due to radiation damage to tumour growth in combination and the other is due to tumour growth alone If for a proportion of the injuries $C_{R T}+C_T$ the C_T components are reduced or eliminated the residue of the complex injury would be interpreted as a radiation injury (R) It is thereby inferred that a transformation from a complex to a radiation injury can occur if alkoxyglycerols are given in prophylactic administration but not if they are given only during and after therapy

The incidence of complex injuries has an additional facet of interest It has namely been found that about 99% of the patients with complex injuries will be dead within five years after the initiation of radiotherapy Thus a decrease of complex injuries would likely correspond to a considerable increase in the five year survival rate Data are available that support this contention

By a comparison of the two intracavitary treatment modalities L and H respectively it is found that the incidence of injuries is considerably higher following the employment of increased rather than conventional amounts of radium This despite the fact that the majority of the patients in the H group (about 85% of them) have received a calculated dose on the bladder wall <5 000 rad and on the rectal wall <4 000 rad This underlines the statement made above that the increased amount of intracavitary radium was used in advanced bulky tumours It is therefore not surprising that the incidence of injuries is more dependent on the amount of radium (times application time) than on the calculated dose contribution to the bladder or rectal walls

One of the most striking effects of prophylactic administration of alkoxyglycerols described in this investigation is that it produced a decrease with more than 60% of the incidence of total injuries (I) in the group treated with increased amount of radium in the intracavitary irradiator

The data described in the study strongly suggest that alkoxyglycerols have two distinct effects inhibition of tumour growth and protection against tissue damage following radiation The study of the so called complex injuries and the comparison between prophylactic and non prophylactic administration of alkoxyglycerols have made it possible to separate these two effects

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PREOPERATIVE IRRADIATION IN STAGE III CARCINOMA OF THE OVARY

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ract A series of 456 patients with malignant epithelial ours of the ovary clinical stage III is presented Of e 96 were initially inoperable and 49 had a clinical osis of inoperable disease at the first examination r 3000 rads external highvoltage irradiation it was d possible to remove the primary tumour the uterus the omentum in 36 (38 %) of the previously inoperable ents. Of the 49 patients who had only a clinical osis of inoperability only four were inoperable at otomy performed three weeks after completion of 0 rads external radiotherapy The five year survival for the whole series was 16 %

e survival of patients with ovarian cancer is de dent upon several factors the stage of the dis e the histological type and grade of malignancy the amount of residual disease after surgery It common situation in referral institutions to see s with ovarian cancer who have had a rotomy with only a biopsy performed due to able disease It has been claimed that even in ents with inoperable tumours as much tumour e as possible should be removed without risk life threatening complications (10) The value of e or po operative irradiation is still under de . This paper reports a prospectively designed dy to determine whether such inoperable pa s would benefit from preoperative external otherapy followed by a second attempt at re al of tumour

MATERIAL

een 1968 and 1973 a total of 1427 patients with gnant ovarian tumours were treated at the Norwegian m Hospital 456 of which had epithelial tumours e III according to the FIGO Classification (7) The ical status of these patients at admission to the hospital en in Table I In one third of the cases it had been possible at the primary surgical exploration to perform so-called complete pelvic surgery total abdominal hysterectomy bilateral salpingo-oophorectomy and omentectomy In another third of the patients only parts of the primary tumour or metastases had been removed and in 21 % of the cases the tumour was found completely inoperable and only a biopsy had been taken A clinical diagnosis of inoperable disease without laparotomy had been made in 49 patients (10 7 %) The clinical examination included chest X ray barium meal and enema intravenous pyelogram proctoscopy peritoneal fluid cytology and/or fine needle aspiration biopsy from the tumour as described by Kjellgren et al (6)

The patients were all caucasians The youngest patient was 21 years and the oldest 77 years of age Distribution by histological type i shown in Table II The age distribution of the patients within the different tumour groups varied little with a mean age between 53 3 and 60 3 years No patients have been lost to follow up and all deaths have been recorded as cancer deaths Cumulative survival curves have been made according to the life table method (2)

Treatment

The 145 patients who were considered inoperable at the admission to the hospital all received 3 000 rads midplane dose supervoltage therapy extending to the T_x–L region The dose was delivered in 18 fractions through parallel

Table I *Clinical material Status at admission to the Norwegian Radium Hospital*

Treatment group	Number	Per cent
Complete pelvic surgery	154	33 7
Partial tumour resection	157	34 5
Inoperable biopsy only	96	21 0
Clinical diagnosis of inoperable disease	49	10 7
Total	456	100 0

Total abdominal hysterectomy bilateral salpingo-oophorectomy and omentectomy

Table II *Distribution by tumour type*

Tumor type	Number	Per cent
Serous carcinoma	256	56
Mucinous carcinoma	55	12
Endometrioid carcinoma	77	17
Other or unclassified	68	15
Total	456	100

Table III *Outcome of second look operation after 3 000 rads external irradiation for 96 patients initially found inoperable*

Type of surgery	Number	Per cent
Complete pelvic surgery	36	37 5
Partial tumor resection	26	27 1
Still inoperable	34	35 4
Total	96	100 0

opposed anterior and posterior portals over four weeks The kidneys were shielded after 2 000 rads Three weeks after irradiation was completed a new attempt at radical surgery was made

RESULTS

The results of postirradiation surgery for the 96 patients that were considered inoperable at the first laparotomy are summarized in Table III In some cases only parts of the tumour masses could be removed and in many cases also the uterus had to be left behind Others were still totally inoperable despite the irradiation In 36 patients (38 %) it was possible to remove the primary tumour the uterus and the omentum (complete pelvic surgery) In another 26 patients (27 %) it was possible to remove part of the primary tumour and metastases In 34 cases (35 %) irradiation therapy had not influence the operability of the tumour

The 49 patients that had only a clinical diagnos of inoperable disease without laparotomy init all all gave the impression of advanced disease. W cannot know for certain whether operability w enhanced by the preoperative radiotherapy should be noted however that there were very fe (4 patients) that were completely inoperable in th group after having received 3 000 rads external r radiation In Table IV this group is compared wi 407 patients who had some type of primary surger performed before admission to the Norwegia Radium Hospital As can be seen only 8 % of th cases diagnosed clinically as inoperable wer found completely inoperable after preoperativ radiotherapy as compared to 24 % of those cas who had surgical exploration before referral to o institution The highest survival rate was foun amongst those patients who had so-called com plete pelvic surgery at the first attempt Conside ing that they all had widespread disease wi metastases to the upper abdomen a five year surv val of 24 % is not too disappointing (Table V) Th corresponding survival rate for those who we considered inoperable at first laparotomy and i whom complete pelvic surgery could be performe at the second look operation after 3 000 rads ex ternal irradiation was 13 % A similar survival ra was found in the group of patients who had a cli cal diagnosis of inoperability before irradiation an the second look operation (15 %) It is hard surprising that the worst prognosis was found in th group of patients who were found to have inoper ble tumour both at the first and second operatio (5 %) Fig 1 shows the survival curves for 154 p tients who had complete pelvic surgery performe at the first operation and for that group of patien

Table IV *Results of first surgical exploration with or without preoperative irradiation*

Type of surgery	No preoperative radiotherapy		Clinical diagnosis of inoperability and preoperative irradiation 3 000 rads	
	No	Per cent	No	Per cent
Complete pelvic surgery	154	37 8	24	49 0
Partial tumour resection	157	38 6	21	42 9
Inoperable	96	23 6	4	8 1
Total	407	100 0	49	100 0

Table V. *Survival rates in relation to treatment and operability*

...atment group	Survival No	1 year (%)	2 years (%)	5 years (%)
...plete pelvic surgery at first laparotomy ...o preoperative irradiation	154	51	3_	4
...perable at first laparotomy Complete ...ic surgery after 3 000 rads	36	4	7	13
...perable at first and second laparotomy ...00 rads between laparotomies	34	8	17	5
...ical diagnosis of inoperability ...00 rads before laparotomy	49	45	3	15

...o were found inoperable both at the first and at second look operation

DISCUSSION

...operative radiotherapy has been strongly advocated by some authors (8 9 12) to enhance operability and to decrease the probability of disseminating tumour at surgery This study demonstrated ...at operability is enhanced by preoperative radiotherapy making possible complete pelvic surgery ...38% of the patients initially considered inoperable. Our protocol included an attitude of aggressive surgery and different surgeons were involved in the ...o laparotomies These facts of course will influence the results and we cannot know how much preoperative radiotherapy has really changed the operability in these patients Furthermore it is interesting to note that only 8% of the patients that had a clinical diagnosis of inoperability upon admission were completely inoperable after radiotherapy This figure should be compared to the 24% inoperability in the 407 patients who had primary surgery elsewhere and who had no preoperative treatment

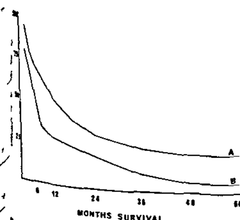


Fig. 1. (A) Survival curve for 154 patients initially operable. No preoperative treatment (B) Survival curve for 34 patients inoperable at first laparotomy 3 000 rads external radiotherapy to large abdominal field before second laparotomy All were still inoperable

This aggressive attitude however has its price Among the 145 patients in the study group there were 13 postoperative deaths giving a postoperative mortality of 9% (defined as death within 30 days of surgery) Treatment of advanced disease of this type carries a high risk regardless of treatment modality This is evident from the steep fall of survival curves in stage III ovarian cancer within the first few months following diagnosis Removing the bulk of tumour is a simple question in patients with small mobile tumours As other authors have recommended (3 11 13) we attempted to remove the uterus both ovaries the omentum and metastases that could easily be taken out Median survival time is believed to be inversely proportional to the bulk of remaining tumour (4) Munnell (10) compared survival rates from 1952–1961 with earlier series and concluded that the improved survival rate was probably due to more aggressive surgery and radiotherapy In the present study many patients had widespread disease throughout the upper abdomen One may question if aggressive surgery is appropriate also for these cases Some feel that so few of these patients can be salvaged that aggressive surgery is not the preferred means of therapy (1 9) Kottmeier (8) makes one exception to the principle of conservative surgery in widespread disease When the tumour is of the mucinous type the response to radiotherapy will be

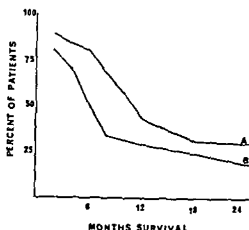


Fig 2 Survival curves for initially inoperable patients (A) 36 patients that had complete pelvic surgery at second laparotomy after receiving 3000 rads external radiotherapy (B) 34 patients inoperable at first and second laparotomy 3000 rads external radiotherapy between laparotomies

less and one should in such cases depend more upon surgery In this study the majority of the mucinous tumours (78 %) were primarily operable and only eight patients in the study group had mucinous tumours None of these patients survived more than 36 months

If five year survival is used as a criterion to evaluate the benefits of aggressive surgery following preoperative radiotherapy we can only show a small increase in salvage rates In those patients who had successful surgery at the second attempt however there was a shift towards prolonged survival for the first two years compared to those that were still inoperable (Fig 2) One can only hope that this brief postponement of death was combined with some degree of palliation of symptoms

It may be concluded that operability is undoubtedly influenced by preoperative radiotherapy but increased survival attributable to aggressive surgery was not as great as anticipated

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VARIATIONS IN PLASMA STEROID AND PROSTAGLANDIN CONCENTRATIONS DURING HUMAN PREGNANCY

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Abstract Radioimmunoassay of sex steroids and prostaglandins was performed on plasma obtained from 10 uncomplicated primigravid subjects at a stated time of the day at varying stages of gestation Prostaglandin E_2 (PGE$_2$) prostaglandin $F_{2\alpha}$ (PGF$_{2\alpha}$) oestrone and oestriol concentrations reached a peak a few weeks before term and then declined Progesterone 17 hydroxyprogesterone and oestradiol increased during pregnancy particularly af[illegible]3 weeks In two normal patients repeated blood samples were taken throughout the day at weekly intervals in late pregnancy for sex steroid assays to evaluate the variation of concentrations with the time of sampling and the significance of changes in mean concentrations of different steroids with approaching parturition Marked variability was found in the levels of different steroids during the day Plasma oestriol values were lowest at 8 00 a m in the patient sampled frequently A marked decrease in oestriol oestrone oestradiol and 17 hydroxyprogesterone was found in one patient prior to the onset of spontaneous labour In another subject there was no decrease in concentrations of oestrogens or progestogens prior to induction of labour at term

Although sensitive radioimmunoassay techniques have been in use for several years there is still no general agreement as to what precise changes occur in the endocrinological status in late pregnancy In some animal species blood progesterone levels fall preceding the onset of labour (8) but only few studies have confirmed this in man (3 10) Oestrogen levels rise towards term and oestradiol promotes prostaglandin synthesis (2) Prostaglandins stimulate the myometrium and enhance and potentiate endogenously released oxytocin (5) However the exact interrelationship and interdependence between the various protein and steroid hormones and prostaglandins during pregnancy is imprecise

This study was undertaken to establish the levels of sex steroids and prostaglandins in uncomplicated pregnancies throughout gestation and particularly to assess whether the results are influenced by the time of sampling Therefore in late pregnancy serial samples were taken from specific individual subjects to help assess this possibility

MATERIALS AND METHODS

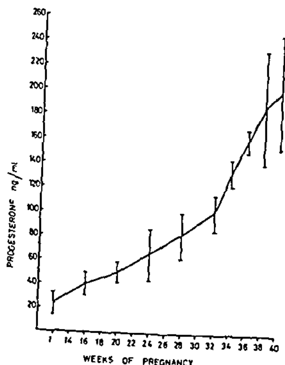
Healthy primigravid subjects with an uncomplicated pregnancy acted in a volunteer capacity Each patient had

Table I *Variations in sex steroid concentrations (with time of sampling)*

Plasma hormone (ng/ml)	Time of sampling				
	8 p m	12 p m	8 a m	1? noon	4 p m
Progesterone	33 2	83 4	52 0	76 4	61 3
17 hydroxyprogesterone	?4 8	22 9	20 0	26 4	24 4
Oestrone	11 4	10 7	13 7	13 0	21 3
Oestradiol	13 7	17 9	14 7	18 8	23 1
Oestriol	7 1	12 3	3 7	10 1	8 1

Lowest value

[illegible]



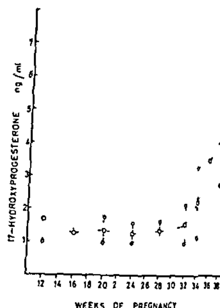


Fig 1 Changes in plasma progesterone and 17 hydroxy progesterone during pregnancy

impeccable menstrual data to indicate that her gestation was correct In each instance there was no discrepancy greater than one week between the clinical evaluation of gestation and the menstrual age of the pregnancy Ten cross sectional samples were taken in routine antenatal clinics between 9 00 a m and 10 00 a m once each month from 12 weeks to 28 weeks After 28 weeks samples were taken at two weekly intervals until 36 weeks and weekly thereafter

In addition two normal primigravid patients acted as volunteers to assess the possible variation in steroid levels with the time of sampling They were admitted at weekly intervals from 35 weeks onwards and an intravenous cannula was inserted into a forearm vein Samples of b were collected four hourly from 8 00 p m on one day 4 00 p m on the following day omitting the 4 00 a m sample The patients were then allowed home

10 ml of heparinised blood was taken from the ant cubital vein by venepuncture or from an intraveno cannula in those patients sampled throughout the hours The plasma was separated following centrifugation and stored at −20°C until assayed Radioimmunoassay of oestrogens progesterone 17 hydroxyprogesterone and $PGF_{2\alpha}$ were as reported previously (11 12 13 14) PG concentrations were evaluated using a technique simil to that of $PGF_{2\alpha}$ (15)

Table II *Variation in progesterone with time of sampling at weekly intervals in late pregnancy*

Gestation (wk)	Time of sampling 8 p m	12 p m	8 a m	12 noon	4 p m
34	48	56	53	46	51
35	93	71	51	62	57
36	93	65	44	54	62
37	33	83	52	76	61
38	159	150	118	122	109
39	116	141	110	130	148
40	164	137	114	161	128

Lowest value

Table III *Variations in oestriol with time of sampling at weekly intervals in late pregnancy*

Gestation (wk)	Time of sampling 8 p m	12 p m	8 a m	12 noon	4 p m
34	2 3	3 3	0 5	1 7	3 7
35	4 6	6 3	2 ?	3 ?	4 8
36	16 3	5 2	4 3	4 ?	5 6
37	7 1	1? 3	3 7	10 1	8 1
38	12 2	7 3	6	8 0	6 ?
39	7 7	14 5	6 6	5 3	13 9
40	7 2	12.3	6 9*	1? 5	14 0

* Lowest value

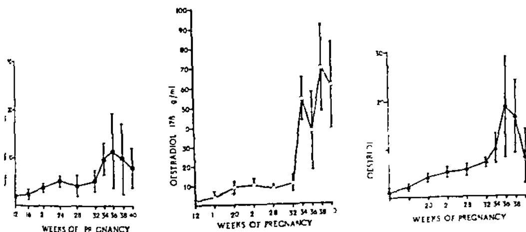


Fig 2 Changes in plasma oestrogens during pregnancy

RESULTS

There was a continuing rise in progesterone levels throughout pregnancy up to term and an increase in 17-hydroxyprogesterone particularly marked after 32 weeks (Fig 1) In this study circulating oestrone and oestriol levels increased to a peak between 34 and 36 weeks and then declined gradually to term (Fig 2) Oestradiol values showed a particular elevation after 32 weeks Prostaglandin E_2 and $F_{2\alpha}$ concentrations similarly reached a peak several weeks before term and then gradually declined (Fig 3)

The variation in steroid concentrations with the time of sampling in a specific patient at 37 weeks is seen in Table I Progesterone levels showed a marked variation throughout the day from 33 2 to 83 4 ng/ml whilst 17 hydroxyprogesterone levels exhibited less fluctuation The variation in oestriol concentrations was twice as great as for oestradiol and oestrone

Variations in the change in concentrations of progesterone from the time of sampling at different weeks of gestation in late pregnancy are seen in the same subject in Table II Four out of seven records were lowest at 8 00 a m and in two of the other three the 8 00 a m value was the next lowest

Variations in the oestriol values in the same sub-

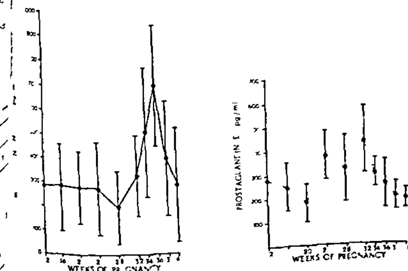
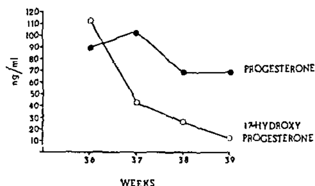


Fig 3 Changes in plasma prostaglandin E_2 and prostaglandin $F_{2\alpha}$ during pregnancy



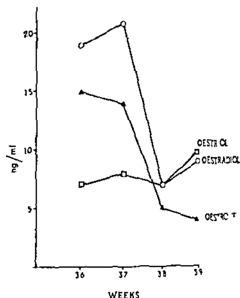


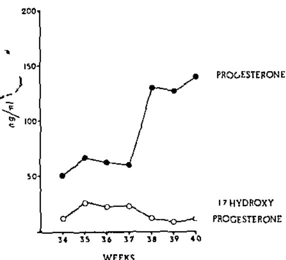
Fig 4 Changes in mean plasma steroid concentrations of serial daily samples preceding spontaneous labour

ject expressed in the same manner are seen in Table III The majority of low values were also found at 8 00 a m

The mean concentrations of the five daily samples taken from two subjects serially sampled at weekly intervals in late pregnancy are seen in Figs 4 and 5 respectively The patient shown in Fig 4 went into spontaneous labour five days after the last sampling 17 hydroxyprogesterone oestrone and oestradiol values declined prior to the onset of spontaneous labour whereas progesterone values remained relatively static In the other subject (Fi 5) labour was induced for social reasons short after term but until this time oestrone oestradi and progesterone continued to rise oestriol a 17 hydroxyprogesterone varied very little

DISCUSSION

Plasma progesterone values increased pregnancy to term and no dramatic decline ... centrations was observed in the two patients se



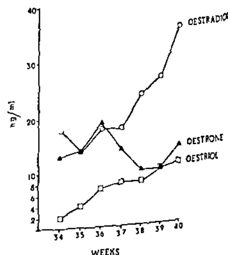


Fig 5 Changes in mean plasma steroid concentrations of serial daily samples preceding induction of labour at term

ly sampled in the last month of pregnancy These findings are contrary to those reported by Csapo (3) and Turnbull (10) but isolated rather than repeated samples were taken in these studies The wide variation found in the samples taken in individual subjects at different times of the day confirm finding previously reported by one of us (1) Collection of samples in the early morning when the concentrations appeared least indicates that this may be the optimal time for sampling if the results are to be meaningful 17 hydroxyprogesterone concentrations varied less throughout the day in individual subjects studied but as with progesterone a continuing upward trend was seen as gestation progressed particularly after 37 weeks as has been reported by (9) The significance of this steroid in pregnancy and during parturition has yet to be evaluated since its production has been largely considered up to the present to be associated with the function of the corpus luteum However the marked decline in mean concentrations of 17 hydroxyprogesterone oestrone and oestradiol in the patient going into spontaneous labour may indicate alterations in the metabolic pathways of these steroids in the foeto placental unit with incipient labour

The finding that there is no significant diurnal variation in plasma oestriol values in human pregnancy is in accordance with another study (7) Oestrogen production by the placenta has been suggested to trigger the synthesis of prostaglandins (2) and PGE_2 and $PGF_{2\alpha}$ concentrations were found to follow the pattern of increase in oestradiol levels after 37 weeks However circulating prostaglandin levels did not remain elevated after 36 weeks but declined possibly due to an effect of high circulating progesterone concentrations or perhaps some yet unisolated lysosome stabilising factor (6) The exact relationship between natural prostaglandins the more stable metabolite 13 14 dihydro 15 keto $PGF_{2\alpha}$ and sex steroids prior to the onset of spontaneous labour in human pregnancy awaits elucidation The variability of results with the time of sampling indicates that there are limitations in interpreting peripheral blood steroid concentrations as either a predictive test of incipient fetal demise or for assessing the likelihood of the onset of parturition. It is therefore not surprising that it is difficult to draw significant conclusions from apparent inter-relationships of different hormones at a site distant from the uterus

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rekommenderar
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Alla nya P-piller-patienter



Neovletta

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Neovletta

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THE CHANGE OF ALKALINE PHOSPHATASE BINDING CONDITIONS WITH TROPHOBLAST MEMBRANE AT DIFFERENT STAGES OF HUMAN PLACENTA

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stract Alkaline phosphatase was brought into solu ns from microsomal fractions of placentas of varying stational age by using gradually increasing concentra teinase papain When the activity of the solu alkaline phosphatase (S) was compared with that of residue (R) the S/R ratio rose as preg y progressed The electrophoretic pattern showed in serum from pregnant women the papain soluble aline phosphatase corresponded to the heat stable one results indicate that the cytoplasmic membrane of trophoblast changes with the growth of the placenta so this enzyme is easily dissolved by papain It is proba that alkaline phosphatase molecules easily enter the rnal blood stream in late pregnancy

man placental alkaline phosphatase activity in serum of pregnant women increases as preg ancy progresses and this phenomenon has been ely used clinically as a test of placental growth nd function as this enzyme is distinguished from ers by its heat stability (1 4 5 6 7 9) As e specific activity of the placental alkaline phatase increases with placental growth the tivity of this enzyme may also increase in mater erum (5) though this relationship has not been oved The alkaline phosphatase releasing e hanism may involve changes in the placental phoblast membrane as it grows since alkaline phosphatase binds to the membrane of the tropho- st (5) In the present study human placental crosomes of varying gestational age were ionated and treated with proteinase papain The ratio of the activity of soluble alkaline phatase to that of the residue bound to miscro- es was calculated Furthermore soluble al line phosphatase was compared with placental alkaline phosphatase in the serum of pregnant women by polyacrylamide gel electrophoresis The re leasing mechanism of this enzyme from the placenta was discussed

MATERIALS AND METHODS

Human placenta Placentas were obtained from cases of normal delivery spontaneous abortion and induced abor tion None of the cases were complicated by for example toxemia diabetes mellitus etc

Microsome preparation All placentas were stocked immediately after delivery in a deep freezer at −70°C and thawed at room temperature for use After thawing they were minced with scissors and washed in 0 9% NaCl solution and blood connective tissue and vessels were removed as far as possible The chopped tissue was homogenized with Teflon homogenizer by five up-and down strokes in 10 mM Tris-Cl pH 7 2 at 0°–4 C The homogenates were centrifuged at 3000×g for 15 min at 4 C and the supernatants were centrifuged again at 105 000×g (R_{max}) for 1 hour at 4 C The microsomal pel lets were suspended in 10 mM Tris-Cl at pH 7 2

Papain treatment to bring alkaline phosphatase into solution Ten ml of papain solution (Merck 3 5 m Anson E/mg in 10 mM Tris Cl pH 7 2) was prepared in gradual concentrations These were added to 0 1 ml of the microsomal fractions (0 63 mg of protein) of varying ages incubated at 36 C for 30 min and centrifuged at 105 000×g (R_m) at 4 C After centrifugation the pellets were suspended in 3 0 ml of 10 mM Tris Cl pH 7 2 Aliquots 0 1 ml of each of the supernatant and pellet suspensions were used for the measurement of the alkaline phosphatase activity by King & Kinds method at pH 10 1 (2)

Determination of protein concentration Protein de termination of microsomes was performed by Lowry s method using bovine serum albumin (type V) as a standard (3)

Polyacrylamide gel electrophoresis 0 1 ml aliquots of

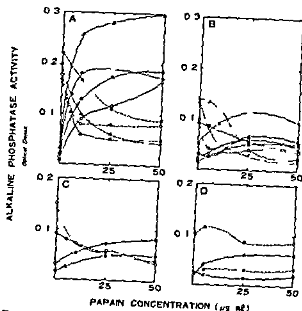


Fig 1 The activities of the soluble alkaline phosphatase and those of the non soluble residue Measurement of alkaline phosphatase activity was performed by Kind & Kings method using wavelength 580 nm The same plot marks represent the same placenta Week of gestation (A) 36–40 weeks (B) 25–28 weeks (× 32 weeks) (C) 21–24 weeks (D) 13–16 weeks — Soluble fraction non soluble residue

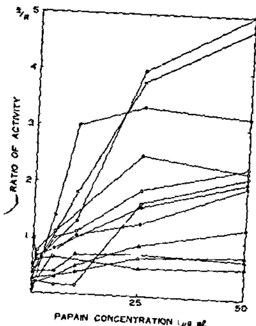


Fig 2 Ratio of activities of soluble alkaline phosphatase (*S*) and that of the non soluble residue (*R*) Aliquots 0 1 ml from 10 ml of soluble fractions and 3 0 ml of non soluble residue suspensions were used for the measurement of enzyme activity The true *S/R* ratio is calculated by multiplying the values in Fig 2 by 10/3 ● 36–40 weeks × 32 weeks ○ 25–28 weeks ▲ 21–24 weeks △ 13–16 weeks

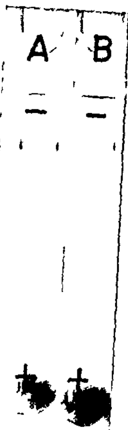


Fig 3 Electrophoretic zymogram patterns of alkaline phosphatase (A) Papain soluble fraction from placental microsome (B) Heat treated serum of a late pregnant woman

papain solubilized solution from the mature placental microsome and the serum of pregnant women were forced onto 7 5 % polyacrylamide gel buffered by 10 mM Tris pH 8 0 and treated electrophoretically at 150 volts for min (The serum was preheated at 56 C for 15 min to inhibit the alkaline phosphatase from other sources) Alkaline phosphatase was stained in the solution containing 10 mM Tris Cl pH 8 5 0 1 mg/ml of alphanaphthylphosphate disodium salt as substrate 1% dimethylformamide and 0 3 mg/ml of Fast blue BB salt (Sigma

RESULTS

Rate at which alkaline phosphatase from placental microsomes of varying age was brought into solution by papain Fig 1 reveals the activity of papain soluble alkaline phosphatase and the non soluble enzyme from placental microsomes of varying gestational age As the placenta grows the activity of soluble alkaline phosphatase rises and reaches a constant value at a low concentration of papain In order to simplify the interpretation

g. 1 the activity of papain soluble alkaline ... (S) and that of the non soluble residue (R) ratio were calculated (Fig 2) Not only does the ... activity of alkaline phosphatase increase ... the S/R ratio also increases with placental growth

Electrophoretic comparison of papain soluble alkaline phosphatase with that in serum of pregnant women To compare papain soluble alkaline phosphatases with that of placental enzyme in the serum of pregnant women both were loaded onto ... polyacrylamide gel for electrophoresis (the serum was pre heated at 56 C for 15 min) The alkaline phosphatase was stained as described in Materials and Methods No difference was found in the electrophoretic distance between papain soluble alkaline phosphatase and the placental enzyme in the serum (Fig 3) Therefore papain soluble alkaline phosphatase from the placenta resembles the enzyme in the serum of pregnant women

DISCUSSION

It is well known that the activity of placental alkaline phosphatase rises in the serum of pregnant women (1 4 5 6 7 9) This enzyme is present in the microvilli of syncytiotrophoblast and increases as gestation progresses (5) The microvilli lie in close contact with the maternal blood and consequently alkaline phosphatase molecules can enter the maternal blood stream via the microvilli (10) ... another mechanism may be considered The present results show that the volume of papain soluble alkaline phosphatase from placental microsomes increases as gestation progresses and the soluble enzyme resembles that from the placenta in the serum of pregnant women in its electrophoretic ... The proteins bound superficially to the cell membrane are reported to be brought in solution by papain (8) Therefore these results indicate that the trophoblastic membrane changes as the placenta grows The binding conditions for alkaline phosphatase molecules to the cell surface change so that the enzyme is more easily brought into solution by papain Probably more alkaline phosphatase molecules on the cell surfaces enter the maternal blood stream in late pregnancy

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HYPERTHYROIDISM DURING PREGNANCY TREATED WITH PROPYLTHIOURACIL

The Significance of Maternal and Foetal Parameters

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Abstract Hyperthyroidism during pregnancy may be dangerous to the infant. The major risks are prematurity and neonatal thyrotoxicosis. The latter may be due to placental transfer of thyroid stimulating immunoglobulins from mother to fetus. Of two siblings of a previously thyrotoxic mother the first had marked symptoms of neonatal thyrotoxicosis after a pregnancy where no antithyroid treatment was given. The second child had only minimal thyrotoxic symptoms but almost as high levels of thyroid hormones as the first. During the second pregnancy propylthiouracil was given to the mother from 26 weeks gestation because of increased fetal movements and fetal tachycardia. Fetal movements and fetal heart rate were considered to be most valuable indicators of thyroid function in the fetus. Intense control is necessary from the the second trimester.

Hyperthyroidism during pregnancy imposes little risk to the mother but it may be dangerous to the fetus and newborn. The incidence of toxaemia has been reported as higher (11). However, the major risks are the marked increased incidence of prematurity with its resultant complications and mortality and the risk of neonatal thyrotoxicosis with a mortality of 16 percent in the described 75 cases (9). The physical signs of thyrotoxic disease in the newborn may be absent at birth but will appear within the first few days or weeks of life. The initial symptoms are restlessness and diarrhoea. Later on the infant may develop tachycardia, tachypnoea, enlargement of the thyroid and exophthalmos. It may fail to gain weight in spite of adequate caloric intake. The disease is often transient and benign but may be lethal with progressing cardiac failure.

Many observations suggest that some humoral factor transferred placentally from mother to fetus is responsible for the symptoms in the infant. Maternal long acting thyroid stimulator (LATS) has until recently been accepted as the pathogenic factor (4, 12). Antithyroid medication during pregnancy may reduce morbidity and mortality substantially (14). However, overtreatment may be dangerous to the fetus with resultant hyperthyroidism with mental retardation and goitre. Most careful physical and laboratory control during pregnancy is therefore essential.

METHODS

Total serum thyroxine concentration (T_4) was assayed using the Thyopac* 5 kit from The Radiochemical Centre Amersham England. Normal ranges were 65–145 nmol/l in adults and 65–175 nmol/l in pregnant women.

Free thyroxine (FT_4) was assayed as normalized thyroxine ratio by the same Thyopac* 5 kit. Normal range in adults and pregnant women was 0 88–1 11 rel U.

Serum triiodothyronine (T_3) was assayed using The Radiochemical Centre's T_3 kit. Normal ranges were 1 3–3 5 nmol/l in adults and 1 5–5 0 nmol/l in pregnant women.

Long acting thyroid stimulator (LATS) was assayed using white guinea pigs (7). In this technique LATS values below 1 25 rel U were normal, 1 25–1 50 was suspected elevated and more than 1 50 was considered significant pathologic.

Fetal heart rate was detected with the Hewlett Packard Cardiotocograph 8071 A Recorder 8025 B.

Fetal movements were judged by external physical examination.

Table I *Second pregnancy Maternal and fetal laboratory and physical parameters before and du treatment with propylthiouracil*

B=birth rel U=relative unit HPL=human placenta lactogen

	Gestational age (weeks)										C
	18	22	24	26	28	30	32	34	36	37 (B)	Bl
T_4 (nmol/l)	264	230	223	269	138	120	130	134	115	169	2
FT_4 (rel U)	1 22	1 16	1 20	1 25	0 98	0 96	0 95	1 0	0 94	1 0	1
T_3 (nmol/l)	>7	>7	>7	>9	4 5	–	5 9	5 1	–	–	1
LATS (rel U)	0 87	0 87	1 40	1 56	0 83	0 76	–	0 76	1 38	1 70	0
U oestriol (μmol/24 h)	–	–	49	73	50	81	95	101	115	–	
S HPL (g/l)	–	–	5 0	3 3	5 3	4 8	5 7	5 3	5 4	–	
Fetal heart rate per min	140	150	155	165	145	140	135	140	140	135	
Fetal movements	0	+	++	+++	+	+	+	+	+	+	
Propylthiouracil (mg/24 h)	0	0	0	300	150	75	62 5	62 5	62 5	62 5	

CASE HISTORY

The mother 27 year old gravida 2 para 2 aborta 0 In 1966 she had undergone partial thyroidectomy for exophthalmic goitre with marked thyrotoxic symptoms She had since been well with no need of antithyroid treatment The exophthalmos persisted and a minimal thyroid enlargement developed again in the years following operation

Non pregnant laboratory data December 1974 T_4 155 FT_4 1 13 November 1976 T_4 143 FT_4 1 10

First pregnancy Girl delivered February 1974 at 34 weeks gestation by Caesarean section indicated by prolapsed umbilical cord During pregnancy no antithyroid treatment was given The mother developed mild preeclampsia in the week preceding delivery Birth weight was 2 050 g and Apgar score was 10 at five minutes Physical examination of the infant revealed staring eyes but no thyroid enlargement During the first week she became hyperkinetic with loose stools At 3 weeks age marked exophthalmos and moderate thyroid enlargement had developed Heart rate was 180–200/min She was treated in an incubator with 30% oxygen and phenobarbital The thyrotoxic symptoms gradually subsided during the following weeks The child was discharged in good condition 50 days old Some exophthalmos persisted but she remained euthyroid

Laboratory data at age 2 weeks T_4 289 FT_4 1 35 TSH<0 4 mU/l (normal) LATS could not be detected quantitatively by the method then available but was found qualitatively

Laboratory data at age 10 weeks T_4 139 FT_4 1 07

Second pregnancy Boy born spontaneously August 1976 at 37 weeks gestation During pregnancy the mother was under strict control in open ward from 18 weeks gestation At 26 weeks gestation the fetus became hyperkinetic with tachycardia recorded by cardiotocograph Treatment with propylthiouracil was started on physical indication (Table I) The further control and medication was based on maternal laboratory data fetal movements and fetal heart rate The mother did not become toxaemic and the circumference of her neck remained the same during the medication The infant was asphyxiated with Apgar score 5 at one minute and ten minutes Birth weight 2 500 g The physical exa tion was normal *During the first weeks he deve* slight lid retraction No other thyrotoxic symptoms noticed No specific treatment was required and the was discharged in good condition when 10 days ol remained well

Cord blood samples including LATS were all norm cord blood (Table I)

Laboratory data at age ? weeks T_4 277 FT 1.36 T LATS 0 90

Laboratory data at age 10 weeks T_4 83 FT_4 0 83

DISCUSSION

The thyroid gland is developed in the first trim from the thyroglossal duct which appears down growth from the floor of the mouth serum T_4 and FT_4 concentrations during no pregnancies are low between 11 and 18 weeks tation and increase progressively between 18 a weeks gestation suggesting rapid maturation c fetal hypothalamic pituitary unit (5)

Maternal T_4 is increased throughout pregn due to an increase in thyroxine binding glo (13) FT_4 remains normal for adults and is then most reliable Maternal thyroid stimulating hor (TSH) increases during the first and se trimesters but returns to normal levels at t Radioimmunoassay of TSH may cross react human chorionic gonadotropin and is therefo limited value

Cord blood samples from normal samples r equal or raised T_4 FT_4 and TSH levels compar maternal blood (6) T_4 and FT_4 are temporarily vated during the first few weeks of life wi

giving rise to any thyrotoxic symptoms in the normal newborn (1 16) In neonatal thyrotoxicosis the increase in the serum levels is higher and of longer duration than the physiologic

Clinical observations seem to indicate that neonatal thyrotoxicosis is due to some humoral factor transferred placentally from mother to fetus Neonatal thyrotoxicosis is closely related to current or previous maternal thyrotoxic disease especially when associated with exophthalmos or pretibial edema in the mother T_4 T_3 and TSH cross the placenta poorly LATS crosses well like other immunoglobulins G LATS has been detected by bioassay in most thyrotoxic infants but not in all (3) Another immunoglobulin of maternal origin human thyroid stimulating immunoglobulin (HTSI earlier known as long acting thyroid stimulator protector' (LATS P)) has recently been detected by radioimmunoassay in thyrotoxic infants where no LATS was found (2 15) HTSI is much better correlated to adult thyrotoxicosis than LATS is (17) These observations are not necessarily contradictory LATS may be an immunologic marker in cases where HTSI is the pathogenic factor and vice versa The two thyroidstimulating immunoglobulins now known may even both be immunologic markers of unknown events The exact pathogenesis remains obscure

In the second pregnancy the fetus became hyperkinetic and developed tachycardia (Table I) The symptoms were regarded as signs of fetal thyrotoxicosis Antithyroid treatment with propylthiouracil which crosses the placenta well was started with immediate clinical and laboratory effect. The fetal thyrotoxic episode retrospectively was shown to be well correlated to *a significant* increase in maternal LATS level LATS bioassay took 4-6 weeks and was therefore of little practical value. Immediately before birth LATS was again raised but maternal T_4 and FT_4 remained normal Cord blood LATS was normal and the newborn was euthyroid with no signs of overtreatment He developed no signs of neonatal thyrotoxicosis except abnormal lid retraction but nevertheless his T_4 and FT values were temporarily elevated and almost analogous to those of his elder sister who was premature and clearly thyrotoxic born after a pregnancy where no antithyroid medication was given The marked difference in clinical symptoms may be perhaps partly due to the peripheral effect of propylthiouracil which has been shown to block the extrathyroidal conversion of T_4 to T_3 the latter being the most biologically active hormone (8)

We suggest that fetal movements and fetal heart rate are most valuable indicators of thyroid function *in the fetus They were found to be reliable and* practical parameters in the control of the hyperthyroid pregnancy and the eventual antithyroid medication The control including serial detections of FT_4 should be strict from the beginning of the second trimester Medical treatment with propylthiouracil until birth without concomitant thyroxine substitution is most logical and the treatment of choice today (7 14) Serial detections of LATS and HTSI should be done if available to support the neonatal paediatric care but at least LATS is of little practical value to the obstetrician

The paediatric aspects of our cases are described in detail elsewhere (17)

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THE EFFECT OF DEXAMETHASONE THERAPY IN PROLONGED PREGNANCY

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Abstract Fifty six patients chosen by random sampling from a total group of 120 post term women received dexamethasone (Decadron® MSD) 2 mg 3 times a day for 4 days, the other 64 patients acting as controls

The evolution of uterine activity was evaluated using pelvic score (PS) and a modified low dosage oxytocin sensitivity test (OST) before (T_1) and after (T_2) the treatment.

During the interval from the second to the 6th day inclusive after T_1 35 women of the dexamethasone group and 15 of the control group had a spontaneous onset of labour (SO) ($0.001 < P < 0.01$)

Five patients in the dexamethasone group with primary rupture of membranes started labour spontaneously within 12 hours after membrane rupture 7 patients in the control group with primary rupture of membranes received oxytocin as labour did not start within 24 hours

Excluding patients artificially induced the mean interval from T_1 to SO was 6 8 days in the control group and [illegible] days in the dexamethasone group ($P < 0.001$)

In both groups PS and the sum of Montevideo units (MU) during OST increased from T_1 to T_2 the increase was significantly greater in the dexamethasone group than in the control group We found no correlation between the results of OST and the T_1–SO interval Dexamethasone as used in this study may promote labour in prolonged human pregnancy Due to its low potency it is not a substitute for oxytocin in the induction of labour

The lowered placento-fetal quotient in the dexamethasone group warrants further study of the effects of steroid hormone on placental function

In some animals corticosteroids have the ability to initiate labour (8) In post term women betamethasone has been shown to promote labour (15) when injected into the amniotic fluid By routine use of corticosteroid hormone induction of labour (IL) the side effects of oxytocin and/or amniotomy (4 10 11 20) could be avoided We report the results of oral administration of dexamethasone to a group of post term women

Patients

Only patients with singleton pregnancies cephalic presentation and without maternal illness or complications of pregnancy were included One patient was excluded because of twin pregnancy another because of hypertonic uterine activity (Fig 1)

Patients who had obviously not reached term were not included Others were excluded as PS initially was too high to permit any appreciable increase Thus a group of 120 post term patients with as much clinical uniformity as possible was selected (Table I) The controls had passed term by 3 days more than the dexamethasone group This fact and the predominance of boys among nulliparous controls may explain the difference between the groups in the babies weight (Table I)

The pregnancies were monitored by frequent amnioscopy assay of estriol excretion and heat stable alkaline phosphatase or placental cystine aminopeptidase in maternal plasma Ultrasound cephalometry was found useful especially to exclude preterm patients

Assessment of PS at the second test (T_2) was the only factor which could be influenced by subjective bias As corticosteroids are known to depress estriol excretion (2 18 21) we did not use a blind study model

The babies weights were recorded to the nearest 5 g placental weight to the nearest 10 g after late clamping of the umbilical cord

Experimental Procedure

The nature of the experiment was explained to each patient She was placed in a comfortable and stable supine position with at least 15 left tilt The pressure receptor of a Malmstrom parturiometer (14) was applied to the maternal abdomen while confirming proper positioning and tightening The air pressure of the parturiometer was recorded by an Elema Schönander transducer EMT35 The signal was written on a Siemens Kompensograph III the

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Abbreviations IL artificial induction of labour MU Montevideo units OST Oxytocin sensitivity test PS Pelvic score T_1 First test T Second test S Spontaneous onset of labour

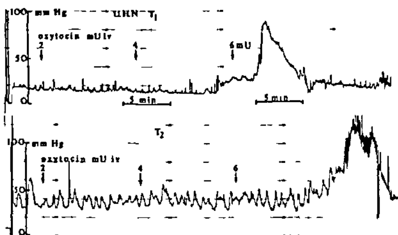


Fig 1 Gravida I 9 days past term
6 During both tests tetanic uterine
traction occurred after 6 mU of oxy
cin Administration of oxytocin w
stopped and tetanic contractions did
recur recording continued for one ho
during both tests Normal vaginal del
ery 5 days after T_2

excursion of the pen having been calibrated against a column of mercury

The oxytocin sensitivity test (OST) of Smyth (10 mU oxytocin intravenously every minute until uterine contraction occurs) seems to reflect myometrial function accurately in terms of its response to the induction of labour (22) As we have witnessed several cases of tetanic uterine contraction while using the oxytocin dosage recommended by Smyth we lowered the dose maintaining the simplicity of the original method

After a control period the patient was given single injections intravenously of 2 4 6 8 10 and 12 mU oxytocin (Syntocinon® Sandoz) at 10 min intervals The activity of the myometrium was calculated in Montevideo units (MU) as the sum of pressure increase in the contractions during each 10 min period disregarding deviation of the pressure curve of less than 5 mmHg The Malmström parturiometer has been shown to give a fairly accurate record of the amniotic pressure during contractions (5) This external method of recording was chosen in order to avoid myometrial stimulation by using an intra or extra amniotic catheter

Using the method of Burnett (3) pelvic score (PS) was assessed after the OST The cervical position effacement dilatation and consistency and the station of the fetal head were given scores 0 1 or 2 the sum or PS ranging from 0 to 10

After the completion of this first test (T_1) the patie
were allocated at random to a treatment group receiv
dexamethasone (Decadron® MSD) 2 mg three tim
each day for 4 days total dose 24 mg the first test d
being the first treatment day Patients allocated to t
control group received no treatment

On the fifth day the OST and assessment of PS w
repeated T_2 We confirmed that dexamethasone had be
taken as prescribed All tests were performed in the mo
ing to avoid the influence of endogenous corticoster
diurnal variation

The patients in the two groups were compared stati
cally with the χ^2 test Differences between the means w
evaluated using t from the formula

$$t=\frac{X_1-X_2}{S\,E}$$

where

$$S\,E_{diff}=\sqrt{\frac{\Sigma(x_1-\bar{x}_1)+\Sigma(x_2-\bar{x}_2)}{(n_1-1)\,(n_2-1)}\left(\frac{1}{n_1}+\ldots\right.}$$

Correlation coefficients were calculated with a d
calculator (Compucorp Statistician) $P<0.05$ was c
sidered statistically significant

)

Table I *Clinical details of patients and babies*

	No of patients	Mean age (years)	Days post calc term at T_1	No of patients with IL	Babies: Boys/girls	Mean weight (g)	Apgar score: 1 min	5 min
Control group	64							
Nulliparae	40	24 5	13 3	11	27/18	3 809	8.5	9 4
Multiparae	24	26 8	11 1	17	14/10	3 619	8 3	9 3
Dexamethasone group	56					560		9.4
Nulliparae	29	24 5	10 8	5	1			
Multiparae	27	27 6	8 0	7	1			

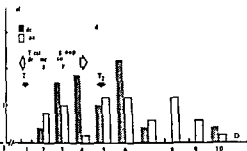


Fig 2 Number of patients with spontaneous start of labour SO each day on the 10 days following T_1 On days 2–6 inclusive 35 dexamethasone treated and 15 control patients started labour spontaneously On days 7–10 in those 4 dexamethasone treated and 13 controls started spontaneously

RESULTS

On the day of T_1 spontaneous onset of labour (SO) did not occur (Fig 2) On the next day dexamethasone seems not to have exerted any effect but on the following days there was a preponderance of SO in the dexamethasone treated patients The dexamethasone effect seemed to last up to and including the 6th day Considering the interval from the 2nd to the 6th day inclusive the number of patients with SO was significantly higher in the dexamethasone group than in the control group ($0\,001<P<0\,01$) During the next 3 days there was a predominance of SO in the control group

Twenty three patients in the control group and 12 in the dexamethasone group had IL (Table II) The mean interval from T_1 to induction was 10 days in the control group and 8 days in the dexamethasone group Four patients in each group were induced before the 7th day after T_1 thus selection due to induction cannot explain the statistical difference

Seven patients in the control group were admitted because of ruptured membranes (Table II) and were given an oxytocin infusion because labour did not start within 24 hours In the dexamethasone group 5 patients were admitted with ruptured membranes in all of them labour started within 12 hours without the aid of oxytocin

Excluding patients having IL the mean interval from T_1 to SO (T_1–SO interval) was 6 8 days in the control group and 5 2 in the dexamethasone group the difference being statistically significant ($P<0\,001$)

Pelvic score

In both groups PS increased from T_1 to T_2 (Table III) the score increase of the dexamethasone group being greater than that of the control group Consistency and effacement were the single factors showing the greatest changes

The mean PS at T_1 in patients with SO before T_2 is not significantly higher than in those in whom labour had not started 5 days later (Table III)

Uterine activity

OST was performed 193 times in the 120 patients Even with our modified OST pathological uterine activity may be provoked (Fig 1)

The uterine activity during T_1 was highest at low oxytocin dosage in patients with SO before T_2 (Table IV) The increase in uterine activity during T_1 was greater among patients in whom labour had not started 5 days later In the dexamethasone group patients with SO before T_2 had a higher sum of MU for the entire test than the others This difference is not found in the control group

Of the 23 control patients with IL 16 had a successful first trial while all the dexamethasone treated women responded favourably to the first trial (Table V) The interval from T_1 to the first trial of IL was shorter in the dexamethasone group and the sum of MU and PS at T_1 was lower in the dexamethasone group than among the controls

Table II *Indications for IL*

	Control group $n=64$	Dexamethasone group $n=56$
Signs of fetal asphyxia		
Meconium stained amniotic fluid declining placental function	2	2
Oligohydramnios	1	
Abnormal oxytocin challenge test		1
Large fetus	5	3
Primary rupture of membranes	7	0
Proteinuria post term pregnancy	1	2
Troublesome pelvic relaxation	3	1
Maternal desire to have the pregnancy terminated	4	3
Total number	23	12
Mean interval from T to IL days	9 9	8 9[a]

Mean interval from T_1 to IL 7 7 days
[a] Difference between the groups not significant

Table III *Mean of pelvic score at T_1 and T_2*

	No of patients	T_1	T_2	Increase (%)
Control group				
Nulliparae				
SO after T_2	25	3 3	4 9	54
SO before T_2	15	3 0		
Multiparae				
SO after T_2	20	3 8	5 6	49
SO before T_2	4	4 5		
Dexamethasone group				
Nulliparae				
SO after T_2	14	3 4	6 3	84
SO before T_2	15	3 3		
Multiparae				
SO after T_2	16	3 4	6 8	100
SO before T_2	11	4 4		

The differences between the control and dexamethasone groups give $P<0\ 001$

Weight of placenta

Mean placental weight in the control group was significantly higher than in the dexamethasone group (Table VI) As the babies of the nulliparae had a higher birth weight in the control group than in the dexamethasone group (Table I) the placento fetal quotient (placental weight−newborn weight)×100 was calculated and found to be significantly higher in the control group than in the dexamethasone group (Table VI) The fall in the placento fetal quotient in the treatment group was related to the treatment period (Fig 3)

Predictive power of OST and PS

Bishop found a correlation between PS and the interval from assessment of the score to the spontaneous onset of labour (1) We correlated the T_1–SO interval to PS and sum of MU at T_1 for each group and both groups together The correlation coefficients were less than 0 3 PS and the sum of MU at T_1 were combined in a scoring system ranging from 0 to 37 There was not correlation between this combined score and the T_1–SO interval In several cases with a relatively high uterine activity which was also regular and increasing during the OST (as in Fig 4) labour was seen to start within a few days so the difference between the mean MU for the two last 10 min periods and the mean uterine activity for the entire OST was calculated It was not correlated to the T_1–SO interval This is in accordance with the results shown in Table IV the increase in MU during T_1 is no greater among those showing spontaneous onset of labour before T_2 than among the others

The standard deviations and coefficients of variation were also calculated they did not show any correlation with the T_1–SO interval

Other findings

The pressure curve of the parturiometer may give some additional information In patients reacting as shown in Fig 1 great care should be taken in the use of oxytocin In most cases slight irregularities tend to become normal with increasing dose of oxytocin If the curve suggests multiple pace maker areas as in Fig 5 the labour may be complicated by dystocia affecting the fetus

Patients having an almost flat contraction curve seldom react favourably to artificial induction during the following week even if they are post term

There were 12 operative deliveries in the control group and 9 in the dexamethasone group excluding these patients the mean duration of labour was equal in the two groups

None of the mothers developed arterial hypertension nor did we recognize any case of infection in the mothers or their babies There was no difference in 1 and 5 minute Apgar score between the groups (Table I)

DISCUSSION

The role of corticosteroids in the evolution of human uterine activity

It has been doubted whether corticosteroids can induce labour in women (9 13) The increased rate

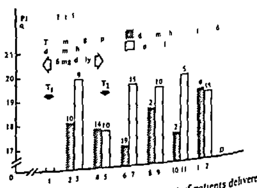


Fig 3 Mean placento-fetal quotient of patients delivered during each time interval Numbers on top of bars denote numbers of patients delivered during each interval

Table IV *Mean uterine activity at each dose level of oxytocin during OST*

	No of patients	Uterine activity MU T₁ 2	4	6	8	10	12	Sum of MU	T₂ 2	4	6	8	10	12	Sum of MU	Increase in sum of MU from T to T₂ (%)
Control group																
Nulliparae																
SO after T_2	25	10	13	18	12	25	25	112	11	15	15	22	26	30	170	7
SO before T_2	15	13	17	12	15	18	19	94								
Multiparae																
SO after T_2	20	9	15	21	24	35	32	135	17	23	38	33	37	39	186	24
SO before T_2	4	16	18	21	25	31	27	137								
Dexamethasone group																
Nulliparae																
SO after T_2	14	8	10	12	15	22	15	82	17	[illegible]	28	32	29	33	161	96
SO before T	15	17	12	20	25	17	29	119								
Multiparae																
SO after T_2	16	3	5	10	7	14	18	57	16	20	26	26	21	30	139	142
SO before T	11	19	24	22	39	41	48	194								

f spontaneous onset of labour after dexamethasone and the shortened T_1–SO interval in dexamethasone treated patients as found in this study show that corticosteroids do accelerate the evolution of uterine contractions Mati et al (15) reached the same conclusion when giving betamethasone into the amniotic cavity Their patients were post term as were ours Gennser et al (9) treating 34 pre term women with betamethasone and comparing them with 17 controls found that the corticosteroid did not influence the duration of

It seems that in women corticosteroids cannot as in sheep (8) initiate labour on their own but that one or more other prerequisites must be fulfilled However the ability of dexamethasone to induce labour is low and its oral administration in the doses used here cannot be a substitute for oxytocin in the induction of labour

In threatened premature labour the plasma progesterone level is lower if the cause is increased primary uterine activity than if it is secondary to cervical incompetence (6) Scommegna et al found decreased urinary pregnandiol excretion after dexamethasone therapy in pregnant women (21)

Recently Flint et al have demonstrated that in the near term ewe dexamethasone given to the fetus increases maternal and fetal plasma 17α 20α-dihydroxypregn-4-en 3-one Simultaneously they found a decrease in the maternal plasma progesterone level (7) They explain the findings as a result of glucocorticoid stimulation of 17α hydroxylase activity leading to conversion of progesterone to 17α 20α-dihydroxypregn-4-en 3-one

Placental weight

Male placentas are slightly lighter than female ones (12) There was a preponderance of boys in the control group (Table I) Difference in sex ratio therefore cannot explain the low placental weight in the dexamethasone group nor can differing maternal height or weight (Table VI) The placento-fetal quotient in the control group is identical with that reported by Hytten (12) The apparent reversible fall of the placento-fetal quotient (Fig 3) does not

Table V *Number of patients responding to first trial of IL and mean T_1-SO interval*

	No of patients	No of patients with successful IL	T_1–SO interval days
Control group			
Nulliparae	11	8	11 1
Multiparae	12	8	9 7
Dexamethasone group			
Nulliparae	5	5	10 2
Multiparae	7	7	8 0

Table VI *Mean weight of placenta placento fetal quotient and maternal weight and height*

	Placenta (g)	Placental weight / newborn weight 100	Maternal Height (cm)	Weight (kg)
Control group	720	19 1	166 1	74 8
S E M	16 2	0 37		
Dexamethasone group	654	17 8	166 9	75 2
S E M	18 0	0 36		

The difference between the groups is significant regarding placental weight and placento-fetal quotient

necessarily imply a causal relationship with the reversible decrease in pregnanediol (21) and estriol excretion (18) after corticosteroid treatment Corticosteroids may reduce the placental weight in some patients who start in labour and reveal a reduced placento fetal quotient while those not responding to corticosteroids (far right columns Fig 5) maintain an unchanged placental weight

Fetal consequences of maternal corticosteroid treatment

We were unable to find any detrimental effect in the babies after dexamethasone treatment as measured by Apgar score (Table I) or observation in the neonatal period by an experienced pediatrician

Brown et al (2) did not find any harmful effects from corticosteroids given continuously or for a short period during the pregnancy However Warrell & Taylor (23) reported 8 stillbirths and 9 fetuses having been at risk during pregnancy or delivery among 34 women treated continuously during pregnancy with prednisolone Failure of placental function seemed to be the common cause but severe maternal disease (bronchial asthma lupus erythematosus arterial hypertension) or complications of pregnancy (pre eclampsia twins failed induction) may have contributed significantly to the results

During pregnancy and especially during l maternal plasma cortisol levels are increased A concomitant increase is found in cord plasm (19) Nwosu et al (17) found that post term postm ture babies had lower morning plasma cortis levels than term or post term (but not post matur babies In another study they found that the po mature babies with low morning cortisol plasma h the same cord plasma cortisol level as the control However the post mature babies lacked the abili to increase the plasma cortisol levels in response distress during labour as did vaginally deliver babies at term (16) The results indicate a relativ adrenocortical insufficiency in the post matu fetus From this point of view corticostero therapy may be a more physiological approa than repeated induction trials with oxytoc or prostaglandins However the influence



Fig 4 Gravida II para I 6 days past term PS 7 B continuation of A Uterine activity is coordinated and increases with increasing doses of oxytocin

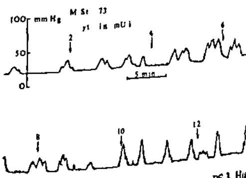


Fig 5 Gravida II para 0 5 days past term PS 3 Hig inc rated uterine activity improving with increas tocin Admitted 3 days later with establish administration or amnioto contractions with Caesarean

corticosteroids on placental weight warrants further studies on the corticosteroid effect on placental function in prolonged pregnancy

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Deklaration
100 g kram innehåller
Miconazoli nitras 2 g
Tefose 63® Labrafil M 1944 CS® paraffinum liquidum acidum benzoicum butylhydroxanisolum
et aqua purificata q s
Egenskaper DAKTAR vaginalkräm innehåller som aktiv substans miconazol ett imidazolderivat Miconazol har såväl in vitro som in vivo fungicid effekt mot flertalet patogena svampar
DAKTAR resorberas i mycket ringa grad vid lokal applikation
DAKTAR har goda kosmetiska egenskaper och innehåller ej lanolin eller parabener Ett fall av sensibilisering har rapporterats Krämen färgar ej kladerna och kan avtvättas med tvål och vatten
Klinik DAKTAR är effektiv vid vaginiter orsakade av Candida spp och andra svampar Såväl mykologisk som klinisk utläkning har konstaterats i ca 90 % av de behandlade fallen Vid behandling med DAKTAR erhålles en snabbt insättande effekt med snabb lindring av symtom som sveda klåda och fluor Behandling med DAKTAR sänker förhöjda vaginala pH värden vilket har en gynnsam effekt på den naturliga bakterieflorans tillväxt DAKTAR lämpar sig väl för behandling av symtomlös vaginit hos gravidae som profylax mot oral mykos hos det nyfödda barnet
Indikationer Vaginiter och vulviter orsakade av jästsvampar
Biverkningar I sällsynta fall (mindre än 1 %) har lätt lokal irritation rapporterats
Dosering En fylld applikator (= 5 g kräm = 100 mg miconazol) töms djupt i slidan vid sänggåendet Behandlingen upprepas dagligen i 14 dagar Det är viktigt för ett gott behandlingsresultat att patienten genomför hela behandlingen Inget uppehåll behöver göras under menstruation Vid graviditet bör applikatorn tömmas långsamt och mindre djupt i slidan Applikator och bruksanvisning medföljer varje förpackning
Forpackningar Tub à 78 g med applikator



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Acta Obstet Gynecol Scand 56 475–478 1977

THE IMMEDIATE EFFECT OF A β ADRENERGIC AGONIST (SALBUTAMOL) ON CARBOHYDRATE AND LIPID METABOLISM DURING THE THIRD TRIMESTER OF PREGNANCY

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Abstract The responses of plasma insulin and the C-peptide of proinsulin glucose lactate free fatty acids (FFA) glycerol D-β hydroxybutyrate and alanine to a β_2-adrenergic agonist (salbutamol) were determined in 5 patients during the last trimester of pregnancy before labor Salbutamol was given as an infusion in the same dosage as is used to inhibit uterine contractions in cases of premature labor and in obstetric emergencies The infusion of salbutamol was given for 45 min accompanied by repeated sampling of arterial blood All patients developed moderate tachycardia and exhibited metabolic effects following salbutamol infusion implying marked increases in plasma levels of insulin C peptide glucose and lactate An increased rate of lipolysis was evident from the rises of FFA glycerol and D-β hydroxybutyrate Plasma levels of alanine declined possibly due to stimulation of gluconeogenesis It is unlikely that these acute maternal metabolic changes would have significant adverse effects on the fetus

In obstetrics there is an increasing use of adrenergic agonists with β_2-rather than β_1 receptor affinity such as terbutaline salbutamol and fenoterol The efficiency with which these drugs induce uterine relaxation has been well documented (1 2 3 4) Cardiovascular side effects have been assessed by the same authors Little attention has however been paid to the metabolic effects on the pregnant women or the fetus The aim of the present study has been to determine some of the maternal metabolic alterations occurring during intravenous infusion of salbutamol in doses compatible with those commonly applied in obstetrical practice

MATERIAL AND METHODS

Five patients with various complicating disorders were studied during the 35th to 38th week of pregnancy (Table I) The investigations were performed with the approval of the regional ethical committee All patients had body weight and height within normal limits None of the patients had uterine contractions and they were all studied after an overnight fast During the investigation the women were in a supine position with the bed tilted slightly (about 15) towards the left side Salbutamol in 0 15 NaCl solution was infused into a brachial vein at a rate of 15 µg/min Heart rate was recorded continuously via a cardiotachymeter triggered by the pulse wave variations in the brachial artery Blood samples were drawn from the arterial catheter before and during the infusion of salbutamol Blood samples were collected in heparinized tubes An aliquot was precipitated immediately in ice-cold 0 6 M perchloric acid for later analysis of lactate (5) while the rest of the sample was stored in ice-cold water Plasma was separated within one hour and was analysed for glucose (glucose oxidase AB Kabi Stockholm Sweden) free fatty acids (FFA) (6) glycerol (7) D-β hydroxybutyrate (8) alanine according to a microfluormetric method adapted after Williamson et al (9) insulin (Phadebas® AB Pharmacia Uppsala Sweden) and C peptide of proinsulin (10) All analyses were done in duplicate

RESULTS

Salbutamol infusion resulted in moderate maternal tachycardia (Fig 1) The heart rate increased from base line values of 93±6 (S E M) to a maximum of 134±4 beats/min Some patients experienced palpitation and slight tremor of the hands during the infusion of salbutamol Parturition occurred 1–4

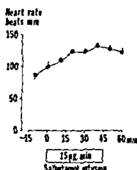


Fig 1 Response of maternal heart rate to intravenous salbutamol infusion (mean values and S E M)

weeks after the investigation with no perinatal complications

The concentrations of metabolites insulin and C peptide in blood and plasma showed significant alterations following the administration of salbutamol (Fig 2 and 3) Thus the concentrations of glucose insulin C peptide FFA glycerol D-β hydroxybutyrate were already significantly ele vated at 15 min lactate at 30 min and alanine showed a significant drop at 30 min (paired *t* test) The mean molar ratios between C peptide and in sulin were 6 7 and 6 0 respectively during the con trol period and declined to 3 8 at 15 min 3 9 at 30 min 4 6 at 45 min and 4 5 at 60 min following the infusion of salbutamol

Statistically significant correlations ($p<0\ 001$) were found between the following parameters C peptide and insulin ($r=0\ 93$) glucose and insulin ($r=0\ 89$) FFA and glycerol ($r=0\ 64$) and FFA and D β hydroxybutyrate ($r=0\ 68$)

DISCUSSION

The doses of salbutamol used in the present study were in the same range as those given to pregnant women by the same route of administration with the aim of inhibiting contractions in cases of prematur labor (2) and in obstetric emergencies (11) All pa tients developed moderate tachycardia in agree ment with earlier reports (2 3 4) but none of them showed evidence of serious cardiovascular side ef fects

The infusion of salbutamol induced a prompt in crease in plasma concentrations of glycerol and FFA (Fig 3) indicating an enhanced rate of lip

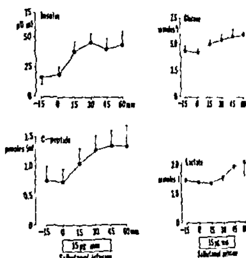


Fig 2 Responses of plasma insulin C peptide gluc and blood lactate to intravenous salbutamol inf s (mean values and S E M)

Table I *Clinical data on the pregnant patients*

Patient	Age	Parity	Gestation at test (weeks)	Complications during preg nancy
AI	18	0	37	Susp placenta praevia
BD	32	1	38	Susp IUGR[a]
BP	23	0	37	Susp IUGR
BB	18	1	35	Proteinuria
MB	37	0	37	Susp placenta praevia

[a] IUGR=intrauterine growth retardation

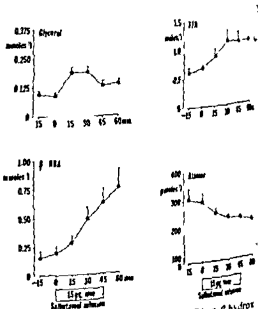


Fig 3 Responses of plasma glycerol FFA D-β-hydrox butyrate and alanine to intravenous salbutamol infusio (mean values and S E M)

mobilization This is in agreement with the β_2 receptor stimulating property assigned to salbutamol The combination of an increased rate of lipid mobilization and marked increments in plasma insulin levels has also been observed in non pregnant subjects following intravenous administration of either salbutamol (12) or isoproterenol a β_1 and β-receptor stimulating agent (13) The parallel increase in plasma levels of insulin and C-peptide—the connecting polypeptide segment of proinsulin—after salbutamol infusion (Fig 2) suggests an enhanced release from the pancreas The calculated molar ratios between C peptide and insulin in plasma in the pregnant women were similar to those observed in nonpregnant subjects (10) After stimulation of insulin release by salbutamol in pregnant women and by oral glucose in non pregnant subjects (10) the corresponding ratios decreased in a similar fashion Previous observations on the effect of salbutamol in dogs (14 15) and in man (12 ...) indicate that the increased insulin release is caused by direct stimulation of pancreatic β_2-adrenergic receptors This interpretation was based on the fact that blood glucose levels either remained unchanged (14 16) or showed only a slight increase which tended to occur after the increase in insulin concentration induced by salbutamol (12) In the present study however we observed a close correlation in time between the rise in plasma levels of glucose and of insulin This discrepancy in results might be due to several factors the pregnant state as such differences in doses of salbutamol ways of administration or different timing of the blood sampling

The elevations of both plasma glucose and blood lactate concentrations induced by salbutamol in the present study could be due in part to an increased rate of glycogenolysis The rise in glucose concentrations might also be explained by increased gluconeogenesis a concept supported by the finding of decreased plasma levels of alanine The steady increase in D-β hydroxybutyrate concentration suggests an increased rate of ketogenesis An increased production of ketone bodies by the liver would be favoured by the accelerated mobilization of free fatty acids and perhaps also by the increased glucagon levels that are known to occur following β-adrenergic stimulation (17)

Infusion of salbutamol in doses used in obstetrical practice induced a series of acute changes in the metabolism of the pregnant woman It is unlikely however that these maternal metabolic changes caused by the salbutamol infusion during a short period would have significant adverse effects on the fetus It has been shown that β receptor stimulating agents are transferred across the primate placenta almost instantaneously and the same group of investigators have demonstrated that an acute effect of the administration to the mother of β receptor stimulating drugs is represented by a diminution of fetal arterial pO_2 (18) In the clinical situation of unwanted labor especially obstetrical emergency however the possible adverse metabolic and circulatory effects on the fetus of β adrenergic agonists must be balanced against the benefit of efficient inhibition of uterine contractions

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OUTCOME OF PREGNANCY IN THE PRESENCE OF INTRAUTERINE DEVICE

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Abstract The outcome of 196 pregnancies with Lippes loop in situ was studied In 102 cases with inaccessible thread the IUD was left in place Ninety four women had the IUD removed when the thread was still visible The incidence of spontaneous abortion and premature delivery was [illegible]6 8% in the group of 102 and was significantly higher than in those women whose loop was removed No serious complications occurred in any of the cases The results suggested that the IUD should be removed early in pregnancy when the string is still accessible

The occurrence of pregnancy following IUD insertion is a distressing problem to both physician and patient especially in countries where induced abortion is illegal This study reports an investigation into the outcome of pregnancy with IUD in situ and the effects of IUD on mother and fetus

MATERIALS AND METHODS

During the period 1968–1975 210 women were diagnosed of being pregnant with IUD in situ at the family planning clinic of Siriraj Hospital In cases where the IUD thread was still visible the IUD was removed by gently pulling the thread If the thread was inaccessible no attempt was made either to remove or locate the IUD All cases were [illegible] followed up in antenatal clinic until pregnancy terminated In those cases whose IUD was not removed [illegible] X ray of abdomen was used to locate the IUD if it was not found during abortion or delivery

Cases of IUD expulsion before pregnancy extrauterine [illegible] and extrauterine pregnancy were excluded from the [illegible]

RESULTS

Of the 210 cases followed there were 4 tubal pregnancies 1 ovarian pregnancy 2 extrauterine IUDs and 7 cases of proven expulsion of IUD before pregnancy (the IUD was not removed and was not recovered during or after pregnancy termination)

The remaining 196 were confirmed cases of intrauterine pregnancy with IUD in situ Of these 196 women 102 had an inaccessible IUD which was left in the uterus (group A) The IUD was removed in 94 women with visible threads (group B) As shown in Table I the accessibility of the thread depended mainly on the length of gestation Of cases seen at 8 weeks pregnancy or less 98 8% had a visible thread This contrasted with 19 1% and 2 1% of the cases seen after a 9–12 weeks pregnancy and after 12 weeks pregnancy respectively who had a visible thread

All patients were using the Lippes loop and size D loop was used in the majority of both groups

Table I *Maturity and visible IUD thread*

	Group A Thread not visible IUD left in situ		Group B Visible thread IUD removed		Total	
Maturity	No	%	No	%	No	%
≤8	1	1 2	80	98 8	81	100
9–12	55	80 9	13	19 1	68	100
≥13	46	97 9	1	2 1	47	100
Total	102	52 0	94	48 0	196	100

Table II *Lippes Loop size*

Lippes Loop (size)	Group A		Group B		Total	
	No	%	No	%	No	%
B	9	8 8	3	3 2	12	6 1
C	28	27 5	31	33 0	59	30 1
D	65	63 7	60	63 8	125	63 8
Total	102	100 0	94	100 0	196	100 0

Table III *Duration of use*

Duration of use (m)	Group A		Group B		Total	
	No	%	No	%	No	%
≤6	21	20 6	6	6 4	27	13 8
7–12	13	12 7	21	22 3	34	17 3
13–18	17	16 7	16	17 0	33	16 8
19–24	14	13 7	14	14 9	28	14 3
>24	37	36 3	37	39 4	74	37 8
Total	102	100 0	94	100 0	196	100 0

(Table II) The duration of use up to the time of conception ranged from 3 to 38 months (Table III) The pregnancy rate cannot be estimated as several cases were referred from other hospitals or health centers

The age groups parity and number of previous abortions are shown in Tables IV V and VI respectively The incidence of abortion was 7 6% and 5 1% of total pregnancies in group A and group B respectively

OUTCOME OF PREGNANCY

In 102 women whose IUD was not removed spontaneous expulsion at 3–4 months gestation occurred in 2 women (2%) whose pregnancy then went to term without complication Ninety eight women (96%) had spontaneous expulsion of the IUD during abortion or delivery Two women (2%) retained the IUD in the uterus after delivery (Table VII)

As shown in Table VIII when the IUD was not removed 45 women (44 1%) aborted spontaneously within the first 12 weeks and 13 women (12 7%) after 12 weeks of pregnancy Two women (2%) had fetal death and delivered prematurely

Table IV *Age group*

Age group	Group A		Group B		Total	
	No	%	No	%	No	%
≤24	32	31 4	26	27 7	58	29 6
25–29	37	36 3	30	31 9	67	34 2
30–34	22	21 6	21	22 3	43	21 9
35–39	8	7 8	14	14 9	22	11 2
40–45	3	2 9	3	3 2	6	3 1
Total	102	100 0	94	100 0	196	100 0

Table V *Parity*

Parity	Group A		Group B		Total	
	No	%	No	%	No	%
1	9	8 8	14	14 9	23	1
2	24	23 5	30	31 9	54	2
3	15	14 7	11	11 7	26	1
4	18	17 6	6	6 4	24	1
5	36	35 3	33	35 1	69	3
Total	102	100 0	94	100 0	196	10

Table VI *Previous abortion*

Abortion	Group A		Group B		Total	
	No	%	No	%	No	%
0	82	80 4	81	86 2	163	8
1	13	12 7	10	10 6	23	1
2	5	4 9	3	3 2	8	
3	2	2 0	–	–	2	
Total	102	100 0	94	100 0	196	10

Premature live birth occurred in 9 women (8 8%
There was one micropthalmos full term fetus

Among 94 women whose IUD was remove there were 21 cases (22 3%) of spontaneous abo tion within the first 12 weeks of pregnancy within 3 weeks after removal of IUD (Table I removal of the IUD might be the cause of abortu in some of these cases Three women (3 spontaneously aborted after 12 weeks of pregnan and over one month after removal Only 4 wom (4 3%) delivered prematurely There were no fe deaths among full term and premature infants

The incidence of abortion and premature labo in group A proved by the Z test to be significan higher than in group B ($P<0\ 05$) No sepsis other serious complications were observed in t two groups

Table VII *IUD status in group A*

Status	No	%
Spontaneous expulsion at 3–4 months pregnant	2	2
Spontaneous expulsion during delivery or abortion or removed during curettage	98	96
Retained in uterus after delivery	2	[illegible]
Total	102	100

Pregnancy

Table VIII *Pregnancy outcome*

Pregnancy outcome	Group A		Group B		Total	
	No	%	No	%	No	%
Full term						
Live birth	31	30.4	62	65.9	93	47.4
Premature						
Live birth	9[a]	8.8	4	4.3	13	6.6
Intrauterine death	2	2.0	–	–	2	1.0
Spontaneous abortion						
≤12 weeks pregnant	45	44.1	21	22.3	66	33.7
>12 weeks pregnant	13	12.7	3	3.2	16	8.2
Induced abortion	2	2.0	4	4.3	6	3.1
Total	102	100.0	94	100.0	196	100.0

[a] One micropthalmos
[b] Including 1 neonatal death from prematurity

DISCUSSION

The results of this study show that the incidence of premature delivery and spontaneous abortion in pregnant women with retained IUD is significantly higher than in those in whom the IUD was removed This finding was similar to those reported previously (1 2 3) Thompson (4) however believed that if the IUD string is visible the IUD is down in the lower uterine segment or in the endocervical canal and that the pregnancy is probably going to survive whether the IUD is removed or not Evidence in the present study on the contrary shows that the visibility of the thread depends mainly on the gestational period Before 8 weeks of pregnancy almost all cases will have visible threads which will become inaccessible when pregnancy is advanced

There were 2 intrauterine fetal deaths which occurred during 28–32 weeks of pregnancy in the unremoved group Whether the IUD was the cause of death in these 2 cases or not is uncertain Fetal

Table IX *Time interval between removal and abortion*

Interval (days)	No	% of total cases removed (94)
≤7	10	10.6
8–14	7	7.4
15–21	4	4.[illegible]
22–28	–	–
>28	3	3.2
Total	24	[illegible]

death might be due to subclinical premature separation of the placenta provoked by the IUD if the placental attachment was above the IUD (5)

There have been several reports concerning haemorrhage and sepsis complicating pregnancies with IUD mostly with Dalkon Shield and to a lesser extent with Lippes loop or other IUDs (4 5 6 7) Amniotic fluid embolism associated with pregnancy with the IUD in situ has also been reported (8 9) To avoid possible serious complications Dreishpoon (7) recommended that early abortion be performed when pregnancy is associated with an IUD however in this study there were nc serious complications observed in either group o patients Therapeutic abortion therefore cannot ye be justified on grounds of protecting the mother's health in countries where abortion is still illegal

In conclusion based on the results of this study when pregnancy occurred with IUD in situ the IUD should be removed as soon as possible if th string is still visible If the string is inaccessible th IUD should be left undisturbed and the patier closely followed up

ACKNOWLEDGEMENT

We wish to express our sincere thanks to Professor Pra' hand Ariyanitr and Mr Anthony Bennett for their help ar to all personnel of Siriraj Family Planning Research Un who assisted the authors in this study

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SCINTIGRAPHIC STUDIES OF UTERINE AND PLACENTAL GROWTH AND PLACENTAL MIGRATION DURING PREGNANCY

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Abstract. Placental scintigraphy with ^{113m}In (Indium) combined with cervical marking with a shielded ^{57}Co radioactive source was used to study uterine and placental growth in human pregnancy and placental location and migration in a total of 176 patients Uterine length measurements can be used for selecting growth retarded cases. There was an approximately constant ratio between placental diameter and uterine length (0 68±0 03) When the placenta was located on the ventral uterine wall low implantation occurred in 61% The corresponding figure for low implantation when the placenta was located on the dorsal uterine wall was 30% The difference was (p...) significant. Placental migration was studied in 20 patients. Significant migration occurred in 11 cases The placental margin closest to the internal cervical os moved outwards about 3 cm on average

Graphic representation of uterine growth has been shown to be of value in monitoning at risk patients (...6) and is therefore a means of reducing perinatal mortality and morbidity For this reason it seemed of interest to measure the size of the uterus and the placenta in patients investigated for placental location. Because of the distension of the lower uterine segment it was suggested (5) that placentas located in the lower uterine segment might migrate away from the internal cervical os during the course of pregnancy A hypothesis which was later confirmed (...).

The present study describes the distribution of the placental site within the uterus the magnitude of placental migration and growth curves of the uterus and the placenta using scintigraphic technique.

MATERIAL AND METHODS

A gamma camera PHo/Gamma III HP Nuclear Chicago) with a diverging collimator was used Every patient was examined from a frontal and a lateral projection (Fig 1) The oscilloscopic view was photographed by means of a polaroid camera after intravenous injection of 1 mCi ^{113m}In The cervical internal os was marked with a ^{57}Co radioactive source as described earlier (8) The length of the uterus was measured in the sagittal plane (Fig 2) The maximal diameter of the placenta and the distance between the caudal margin of the placenta and the cervical marking was measured The center of the placenta with respect to location in either of the two upper or the two lower quadrants in the frontal projection and on the ventral or dorsal wall in the lateral projection was recorded As the collimator was of a diverging type it was necessary to use a correction factor in order to convert the figures obtained from the polaroid picture into centimeters The correction factor varied in relation to the distance (Fig 3) The average distance A in Fig 1 i e the distance from the collimator to a plane in the patient through the ^{57}Co-marker was about 20 cm A variation of ±1 cm from the average distance implies an error in the correction factor of ±3%

176 patients were examined The reasons for investigation were vaginal bleeding 117 abnormal presentation 17 examination prior to amniocentesis 15 abdominal pain 10 retarded fetal growth 5 and miscellaneous 12 19 patients were examined on two occasions and one patient on three occasions during the course of the same pregnancy The growth curves were constructed from 136

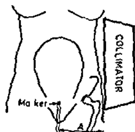


Fig 1 Variation in distance between collimator and cervical marker in the lateral projection Gestation in weeks 19–4? $A=20\ 7\pm2\ 8$ (S D) cm $N=87$

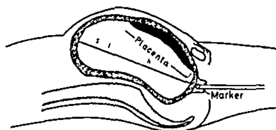


Fig 2 Method of measuring uterine sagittal length and largest placental diameter

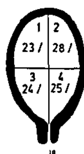


Fig 5 Distribution of placental sites in 4 quadran frontal projection

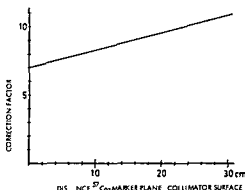


Fig 3 Correction factor in relation to distance between radionucleide and collimator

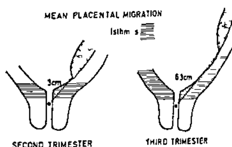


Fig 6 Mean placental migration in 11 patients

results obtained in patients delivered of a normal for date infant i e within ±2 S D of the mean for weight and length (1)

RESULTS

Placental localization The distribution of dorsally and ventrally situated placentas in the four quadrants of the uterus is shown in Fig 4 With 80 located on the ventral wall and 96 on the dorsal wall there was no tendency towards favouring of either location In the total number studied 51% placentae were situated in the upper quadran 49% in the lower quadrants (Fig 5) Of the ally situated placentas 61% were located lower part of the uterus while only 30% dorsal placentas were in this situation the ence is statistically significant ($p<0.001$)

Placental relationship to the internal cervi Patients ($n=20$) examined on two or more occ during the course of the same pregnancy w

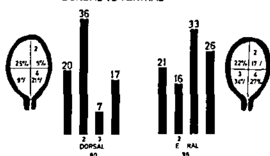


Fig 4 Distribution of placental sites in the dorsal and ventral parts of the uterus

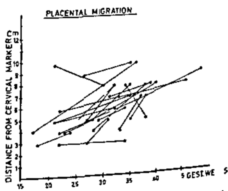


Fig 7 Placental migration in the individual pa relation to gestation

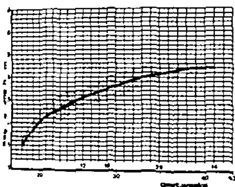


Fig 8 Uterine length in the sagittal plane (Mean ±1 S D) in relation to length of gestation

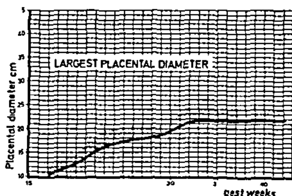


Fig 9 Largest placental diameter (Mean ±1 S D) in relation to length of gestation

...red at intervals varying from 3 to 19 weeks In 13 of these repeated examinations we noticed an increase in the distance from the placental margin to the cervical marking In 11 examinations the distance increased more than 1 cm and on average increased by 3 3 cm (Fig 6) In one the distance was unchanged and *in two it was decreased In the* two latter cases the distances at the first examinations were 8 and 10 cm respectively (Fig 7)

Uterine and placental growth curves Fig 8 shows the growth curve of the uterus obtained by scintigraphic measurement of its sagittal length The growth curve of the placenta has a slightly different shape (Fig 9) The *ratio between placental* diameter and uterine length was fairly constant throughout pregnancy (0 68±0 03)

DISCUSSION

The indication for scintigraphic examination in this study was a pregnancy complicated by one or more factors Vaginal bleeding was the reason for investigation in no less than 67% of the patients This accounts for the fairly high frequency of placentas situated in the lower segment of the uterus (49%) A ...ent pattern has been described in another study (3) This study has shown that there is a tendency for the placenta to be implanted either in the upper dorsal part or in the lower ventral part of the uterus The cause of this is unknown

The reason why the placentas implanted in the lower part of the uterus migrated away from the ... with advancing gestational age is probably due to the continuous enlargement of the isthmus during pregnancy Thus a placenta praevia diagnosed in the second trimester can develop into a marginal or low implanted placenta in the third trimester Consequently there is a progression towards a lower obstetrical risk group It is therefore reasonable to reexamine patients with placenta praevia diagnosed in early pregnancy

The uterine growth curve appears to be of value in assessing fetal growth retardation Three out of four small for dates infants had uterine length measurements well below mean −2 S D This is not unexpected since there is a close correlation between the length of the uterus and the fetal crown rump length (CR) Calculation from available data on CR (7) *shows that the CR is 80% of the uterine* length at 26 weeks gestation and at the 35th week of pregnancy is 90% At 40 weeks both measurements are equal

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FETO MATERNAL BLEEDING

During Pregnancy and at Delivery

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Abstract Blood samples from pregnant women and from mothers before and after delivery were tested for the occurrence of feto-maternal bleeding (f m b) using Kleihauers acid-elution technique and a counting technique described by Schneider It was assumed that f m b had occurred when there was a clinically significant difference between the values of hb-F cells per million cells in two blood samples F m b had occurred in nearly 2/3 of the mothers after pregnancy and delivery The f m b s were most often less than 0 1 ml and only a few per cent had f m b s between 0 1 and 1 ml Abortion complicated pregnancies amniocentesis pre-eclampsia caesarean section and other kinds of complicated deliveries increased the risk of especially larger f m b s

The blood from the fetus is normally separated from the mother's blood by a membrane in the placenta However fetal red cells can pass this membrane as shown by Chown (4) Zipursky (26) was the first to use the simple acid elution method described by Kleihauer (11) for the detection of fetal red cells in maternal blood Since then several investigations of the occurrence of feto maternal bleeding (f m b) have been performed

In nearly all the published investigations the occurrence and amount of f m b have been measured *on the basis of the number of haemoglobin F* containing red cells (hb-F cells) in a single blood sample However a better estimate of the occurrence of f m b and exactly when it occurs can be made by counting hb-F cells in blood samples taken at different times The aim of the present study has been to investigate the occurrence of f m b in connection with various obstetrical conditions counting hb-F cells in blood samples taken before and after these obstetrical conditions

METHODS

The hb-F cells in maternal blood were found by Kleihauers (11) acid-elution technique used in a slightl modified way (7) The hb-F cells were counted as de scribed by Schneider (22)

On the basis of the statistical analysis of the accuracy o the counting method it was decided that two values o hb F cells/million show a clinically significant differenc when one of the values is 0 and the other more than 3 o when one of the values is greater than 0 and the other 50 % higher and at least 10 (7) If a clinically significant differ ence in hb-F cells/million was obtained by counting cel from two different blood samples from the same womar and the higher value was obtained in the second bloo sample it was assumed that f m b had occurred in th period between the withdrawal of the two blood samples

The volume of the f m b was calculated as described b Kleihauer (10)

MATERIAL

Pregnancy The series consists of 225 normal (23) pre nant women all delivering an ABO compatible chil They were asked to come to the hospital once ever month from the third month of pregnancy until deliver In 337 cases we have succeeded in obtaining 2 bloo samples with an interval of 1 month If there had been a f m b it was assumed to have occurred in the mont *when the first blood sample was taken In 24 instances* blood sample was taken in the 9th month of pregnancy a just before labour Blood samples were also taken from pregnant women with pre-eclampsia

Abortion Blood samples were taken from 55 wom just after spontaneous abortion and from 186 wom before and after induced abortion ABO-incompatib cases were not excluded from these groups because t fetuses were not ABO grouped

Amniocentesis Blood samples were taken just befo and 1–7 days after amniocentesis done in 54 normal pre nant women delivering an ABO compatible child N

Table I *Occurrence of feto maternal bleedings*

F m b (ml)	Pregnancy 2nd trim	3rd trim	Total	Induced abortion	Amniocentesis 3rd trim Normal	Compl	Total	Delivery Normal	Caesarean section	Other compl	T
0	139	165	304	154	69	6	75	61	31	11	1(
<0 1	9	18	27	23	3	0	3	6	6	1	
0 1–1	3	3	6	6	1	3	4	3	3	2	
>1	0	0	0	3	1	2	3	0	4	0	
Total	151	186	337	186	74	11	85	70	44	14	1.
	%	%	%	%	%	%	%	%	%	%	%
0	92	89	90	83	93	55	88	87	70	79	8
<0 1	6	10	8	12	4	0	4	9	14	7	1
0 1–1	2	2	2	3	1	27	5	4	7	14	
>1	0	0	0	2	1	18	4	0	9	0	
Total	100	101	100	100	99	100	101	100	100	100	9

of the mothers were Rh immunized All the amniocentesis were done in the third trimester

Delivery Blood samples were taken before (less than 24 h before delivery but before second stage pains) and after 70 normal (23) and 58 complicated deliveries All cases with ABO incompatibility and Rh negative mothers with Rh positive children were excluded (8)

RESULTS

Pregnancy F m b was found in 8% per month in the 2nd trimester and in 12% per month in the 3rd trimester indicating a slight increase in the tendency to f m b during pregnancy (Table I) F m b in the 6th–9th months was seen in 6 (43%) of 14 samples

Table II *Occurrence of hb F cells per million red cells from maternal blood before and after abortion*

b-F sl ion	Spontaneous abortions (After)	Induced abortions Before	After
0	36	160	102
1– 2	12	15	33
3– 9	7	8	33
10–19	0	2	8
≥20	0	1	10
Total	55	186	186
	%	%	%
0	65	86	55
1– 2	22	8	18
3– 9	13	4	18
10–19	0	1	4
≥20	0		5
Total	100	99	100

from pregnant women with pre-eclampsia This significantly ($p=0\ 0056$) more frequent than women with a normal pregnancy where it was se in 10 (9%) of 111 samples taken in the same mont of pregnancy

Abortion After 55 spontaneous abortions in t 1st trimester hb F cells were found in 35% This significantly ($p<0\ 01$) more frequent than in a co trol series consisting of normal pregnant wom tested in the 1st trimester before induced abortio (Table II) The amounts of hb F cells correspond to f m b s below 50 μl

F m b occurred in 17% of 186 women in connec tion with induced abortion in the 1 st trimester Th f m b was between 0 1 and 2 ml in 5% (Table I The occurrence of f m b was apparently not de pendent upon the method used for the ind abo (suction curettage intra amniotic injection or am niotomy)

Amniocentesis F m b occurred in connectio with 6% of 74 normal amniocentesis but in 45% c 11 complicated amniocentesis (blood in the syr inge) which is significantly ($p=0\ 0005$) more fre quent than in normal amniocentesis (Table I)

Delivery After normal deliveries f m b s wer found in 13% and the bleeding amounted to mor than 0 1 ml in 4% After caesarean section f m b were found in 30% of 44 mothers and the bleeding amounted to more than 0 1 ml in 16% which is significantly ($p=0\ 02$) more frequent than after normal deliveries After other kinds of complicated deliveries f m b s were found in 21% and the bleeding amounted to more than 0 1 ml in 14% (Table I)

DISCUSSION

F m b s can easily be detected and measured using the acid-elution method (10) If a sufficiently large number of red cells from maternal blood are looked upon (more than about 1 million) it is possible to detect bleedings as small as 25 μl (5 hb-F cells per million maternal cells) The result is most unambiguously indicated as hb-F cells per maternal cells or as f m b Cases with blood group incompatibility between mother and fetus should be excluded from the study Such incompatibilities will give a greatly reduced survival time of the fetal red cells in the maternal circulation Therefore in these cases a f m b will be estimated to be too small or even not be detected at all (6) In the following only cases satisfying these criteria will be discussed

Pregnancy F m b is theoretically possible from the 4th week of pregnancy when the fetal and the maternal blood circulations in the placenta have been formed However occurrence of hb-F cells in maternal blood from mothers in the 1st trimester cannot immediately be taken as evidence for a f m b because pregnant women in the 1st trimester have an increased production of haemoglobin F (12 20) The same is not the case in the 2nd and the 3rd trimester

In the present investigation f m b could be found in 8% per month in the 2nd trimester and in 12% per month in the 3rd trimester indicating a slight increase in the tendency to f m b during pregnancy The f m b s were mainly small bleedings only 1% amounted to 0 1–1 ml The fetal red cells will survive in the mother for 3–4 months Therefore hb-F cells will be found in an increasing number of mothers during pregnancy On the basis of the occurrence of f m b s per month one would expect that a little less than 44% (8+12+12+12% in the 6th 7th 8th and 9th month and some of the f m b s will occur in the same woman) will have hb-F cells in their blood just before delivery Investigation of blood samples from 150 women in the 9th month showed that hb-F cells were found in 39% of the samples (6)

In women with pre eclampsia a significantly higher tendency to f m b was found in the 3rd trimester This is in accordance with previously published investigations (1 21 27)

Abortion After the 1st trimester spontaneous abortions a significantly larger number of women with hb-F cells was found than in normal pregnant women in the same period of pregnancy In none of the cases was it possible to detect hb-F cells corresponding to a f m b of more than 0 1 ml The same result was found in other investigations where the material included a control group of normal pregnant women in the same period of pregnancy (1 9 14 18)

After induced abortions f m b was found in 17% and in 5% it amounted to between 0 1 and 2 ml In previously reported investigations f m b was found in 3% and 7% (>0 25 ml) and in 3% and 13% (>0 1 ml) (16 24 18 1) The present series was not large enough to show any significant difference between the occurrence of f m b after induced abortion using different methods

Amniocentesis F m b bleeding was found in 6% after a normal amniocentesis and in 45% after a complicated amniocentesis showing the enormous risk of f m b during amniocentesis Previously described cases have all consisted of Rh immunized women with Rh positive fetuses Despite this f m b was also found in 8–11% of the women in these series (1 3 13 19 25 28)

Delivery During delivery the membrane that separates the fetal and the maternal circulation is broken This increases the risk of f m b After delivery there is also a possibility of f m b by the transperitoneal route through the abdominal cavity (5)

Investigation of samples taken before and after a normal delivery showed that f m b occurred in 13% None of the bleedings exceeded 1 ml In previously published series excluding cases of ABO incompatibility an increased amount of hb-F cells was found in 11% (21) Series including complicated deliveries showed increased amounts of hb-F cells in 25% 28% and 26% (2 15 1) In connection with complicated deliveries f m b was found in 30% of 44 cases with caesarean section in the present series This is significantly more frequent than after normal deliveries In 9% of the cases there was a f m b of more than 1 ml After other kinds of complicated deliveries f m b was found in 21% but none of more than 1 ml Montague (17) found f m b s of more than 0 25 ml in 30% of women with complicated deliveries

F m b occurs very frequently even in normal pregnancies and deliveries During the last 6 months of pregnancy it occurs in 10% per month more frequently in the 3rd trimester than in the 2nd trimester and after delivery a further 13% have had a f m b So before delivery half of the

women have had a f m b and after delivery 2/3 Complicated pregnancies and deliveries increase the risk of f m b F m b is thus seen in at least 6% after amniocentesis in 17% after induced abortion in 43% of mothers with pre eclampsia in 30% after caesarean section and in 21% after other kinds of complicated deliveries

The amount of the f m b is normally less than 0 1 ml and in only a few per cent of the cases is it between 0 1 and 1 ml However complicated preg nancies and deliveries increase the risk of larger f m b s F m b s of more than 1 ml were thus only seen after induced abortion amniocentesis and caesarean section but it was still not very common

For the fetus these small f m b s are of no im *portance It is only the very seldom occurring large* f m b s which involve a risk for the fetus How ever for the mother even these small bleedings will involve a high risk of immunization against fetal antigens

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A COMPARISON BETWEEN THE LECITHIN/SPHINGOMYELIN RATIO AND THE NILE BLUE SULPHATE TEST IN THE ESTIMATION OF FETAL MATURITY

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Abstract Functional fetal maturity was assessed in 72 patients by measuring in amniotic fluid the lecithin/sphingomyelin ratio and the differential cell count The correlation between these two tests is presented Only one fetus with a lecithin/sphingomyelin ratio of 2 or more developed the respiratory distress syndrome after delivery that was the child of a diabetic mother The technical limitations of the lecithin/sphingomyelin ratio meant that it could not be measured in 12% of samples obtained

The L/S ratio of amniotic fluid is a measure of fetal pulmonary maturity It is an index of the concentration of dipalmitoyl lecithin which is the major surface active agent in the mature lungs (9) A baby born before it has the capacity to synthesize sufficient dipalmitoyl lecithin is likely to develop the respiratory distress syndrome (RDS)

The Nile blue sulphate (NBS) test is thought to give a measure of the functional maturity of sebaceous glands (4) Cells from the glands are found in amniotic fluid and the percentage stained orange by the dye increases with gestational age

This paper compares the L/S ratio to the NBS test and examines their use in the management of a planned delivery

PATIENTS AND METHODS

The series comprises 72 consecutive patients in whom induction of delivery was contemplated Seventy five samples of amniotic fluid were collected by transabdominal amniocentesis

Each sample was evaluated by both the L/S ratio and the NBS test The obstetric management of the patients was then conducted with full reference to the results obtained

Lecithin/sphingomyelin ratio

The L/S ratios were determined by a modification of the method of Gluck & Kulovich (9) Two ml of centrifuged amniotic fluid were submitted to solvent extraction and acetone precipitation The extracts were chromatographed using the system of Coch and co-workers (2) The spots were visualized by spraying with 10% aqueous ammonium sulphate followed by charring by heating at 250°C for 15 min The lecithin and sphingomyelin spots were measured in two dimensions and the results were reported as lecithin sphingomyelin area ratios By the use of standard dipalmitoyl lecithin and sphingomyelin a linear relationship was found between spot "size and phospholipid concentration over the range normally encountered (10–100 μg)

An L/S ratio of 2 0 or greater is said to indicate functional maturity of the fetal lungs With ratios of less than 1 5 the incidence of significant respiratory distress is 100% When the L/S ratio is 1 5–2 0 some patients develop respiratory distress but much of it will be mild (7)

Amniotic fluid cytology by the Nile blue sulphate stain

All samples were analysed within 24 hours of being taken and interpreted according to the criteria of Husain & Sinclair (10) and Brosens & Gordon (1) (Table I)

Clumping of the cells is a technical problem which affects the cell counting as recognized by Brosens & Gordon (1) In one case there was a *fall* from 15 to 5% orange staining cells in samples taken 2 weeks apart due to this effect

The neonates

The maturity of all babies was assessed clinically by a member of the medical staff within 24 hours of birth

RESULTS

The results of the tests on the amniotic fluid samples are shown in Fig 1 This indicates the correlation between the L/S ratio and the NBS test

Table I *The interpretation of the Nile blue sulphate test*

After Brosens & Gordon 1966

Percentage of cells staining orange	Gestational age (weeks)
0–1	0–34
1–10	34–38
10–50	38–40
>50	>40

The 72 mothers in the series were delivered of 74 babies there being two sets of twins The mean birthweight was 3 23 kg (7 lb 2 oz) with a standard deviation of 0 4943 and a coefficient of skewness of 0 1697 This result does not differ significantly from the zero coefficient of skewness of a normal distribution ($P<0\ 05$) (16) and suggests that the babies represented a normal sample

Respiratory disorders developed in 3 neonates one pneumomediastinum one primary pulmonary atelectasis and one case of RDS

Case report of the respiratory distress syndrome

This was the second child born to a 25 year old Caucasian mother The mother is a diabetic who requires insulin only when pregnant to a maximum dose of 40 units per day The diabetes is controlled by diet alone when she is not pregnant This pregnancy was otherwise normal Radiological assessment of fetal maturity at 37 weeks gestation showed a baby of 36–37 weeks maturity The results of amniocentesis one week later were L/S ratio 2 5 NBS test 22% orange staining cells=38–40 weeks maturity

Labour was induced by artificial rupture of membranes at 38 weeks on the basis of these results The labour did not progress well and monitoring of the fetal heart rate fetal distress

A baby weighing 3640 g (8 lb) was delivered by Caen section with the umbilical cord once round its neck He was resuscitated at birth with the aid of endotracheal intubation The Apgar scores were 2 at 1 min 4 at 5 min and 8 at 15 min Regular respirations were established at 14 min and the baby was extubated at 21 min after delivery

The respiratory rate was 60 per min at 6 hours after birth and a chest X ray showed a slight air bronchogram Despite a further slight rise in respiratory rate and some auscultatory gruntings the baby remained pink in air and gradually improved The baby also required treatment for hypoglycaemia hypothermia and mild jaundice

In summary this was the child of a diabetic mother that suffered fetal distress in labour and was delivered by Caesarean section It subsequently developed definite mild RDS (as confirmed by consultant paediatric opinion) despite a mature L/S ratio of 2 5 and an NBS test of 22% orange staining cells both estimated 7 days before birth

DISCUSSION

The most important investigations in planning an elective delivery are those which measure fetal physiological maturity Tests which measure fetal size or body mass are less useful

The L/S ratio measures the maturity of the fetal lungs and this is the limiting factor in the survival of the premature baby We compared the L/S ratio to the NBS test and found a significant correlation Quinlivan et al (15) found that creatinine and lipid containing cells (stained with oil red 0) were more reliable in predicting fetal maturity than the L/S ratio Kalbac et al (11) found the L/S ratio to be the best creatinine next best and the NBS test the worst However both these investigations compared the laboratory tests to gestational age computed from the menstrual history rather than assessing the status of the baby produced

It is useful to have more than one test available for the assessment of fetal maturity as technical factors may interfere with the laboratory analysis Blood or meconium was present in 17% of the original samples of amniotic fluid and this is known to invalidate the L/S ratio In such cases reliance

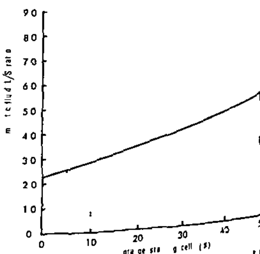


Fig 1 Graph of L/S ratio vs Nile blue sulphate test L/S ratios obtained for 75 amniotic fluid specimens are plotted against the percentage of cells staining orange with Nile blue sulphate All results with more than 50% orange staining cells have been graphed as 50% r 0 50 ($p<0\ 001$) The line of regression of Y upon X has been plotted

would have to be placed on the NBS test which is unaffected by such factors The counting of orange staining cells in the NBS test can however be influenced by *clumping* of the cells

The outstanding situation in which rogue results seem to occur is in some cases of maternal diabetes mellitus There was one such case in our series which developed RDS despite a mature L/S ratio Previous investigators have found similar cases (3 5 6 8 12 13 14 17) and it has been suggested by Whitfield et al (17) that the L/S ratio might fall from a mature value in the interval between amniocentesis and delivery of the baby

With the exception of this one case RDS was successfully avoided in 72 induced deliveries The L/S ratio and the NBS test were shown to correlate significantly with each other and to assist in planning the date of delivery

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SERUM HCG AND HPL IN TWIN PREGNANCIES

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ct Serum HCG and HPL levels were determined samples derived from 39 twin and one triplet ncies Compared with singleton gestations these were respectively 2 5 and 1 5 times higher through tation Analysis of these data in terms of predictive cy for the existence of a twin indicates that neither serve for screening purposes though simultane termination of HCG and HPL may provide a fair f suspicion

vailability of radio immunological methods measurement of placental protein hormones ated interesting applications in the field of l obstetrics The quantitative assay of serum is currently used for the early diagnosis of and extra uterine pregnancies for pre the outcome of threatened abortion for the is and follow up of patients with trophoblas eases and for monitoring cytotoxic drug used for treating these diseases Measure serum levels of HPL is used for the assess placental function during the last trimester

se there is a correlation between placental and the serum concentration of placental es higher levels of both HCG and HPL be expected in multiple gestation They have been reported by a number of investigators mainly in a limited number of cases To question of the degree to which HCG PL assay might contribute to the early detec f multiple pregnancy serial determinations be performed in a sufficient number of pa

PATIENTS AND METHODS

HCG levels were determined by radio-im ssay using the dioxane precipitation method (5) ults being expressed in terms of the 2nd International Standard HCG (MRC London England) For the determination of HPL a double antibody radio immunoassay technique was used (HCS Sclavo Sorin Kit) All assays were performed in duplicate and serum samples were appropriately diluted with phosphate buffered saline containing 1% bovine serum albumin to permit reading from the straight portion of the dose response curve For both hormone assays the mean inter assay coefficient of variation was 9%

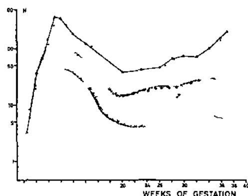
Because the HCG and HPL levels tend to have a log normal distribution throughout gestation statistical analysis of the data was performed accordingly For HCC the geometric mean (±1 S D) of normal singleton pregnancies was calculated from 1540 determinations in 830 women with known LMP for HPL the calculations were based on 632 blood samples taken in 362 pregnancies In 39 twin pregnancies and in one triplet gestation the serum levels of HCG and HPL were determined on at least two occasions Preterm delivery occurred in 9 of these patients Because the hormone levels characterizing the latter group were not divergent from those observed in the pregnancies carried until term (≥38 menstrual weeks) the twin data were pooled

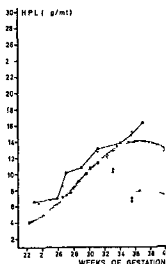
RESULTS

The individual levels of serum HCG and HPL are shown in Figs 1 and 2 The mean values calculated for two week intervals from the 25th week of gestation onwards were significantly higher in twin pregnancies At the 36th week of gestation the mean (±1 S E M) values of HCG and HPL amounted respectively to 39 1±6 4 IU/ml and 14 7±1 2 μg/ml as against 14 5±3 1 IU/ml and 10 7±0 5 μg/ml in singleton pregnancies

Among 29 same sex twin sets (16 female and 13 male) 9 proved to be monozygotic No in the mean serum levels of either or H according to zygosity was observed

In contrast with singleton gestation the maternal HCG level w be higher for female conceptuses





Figs 1 and 2 Serum HCG and HPL levels determined in 39 twin pregnancies Shaded areas represent the geometric mean ±1 S D of the normal singleton pregnancies The solid line connecting the triangles indicates the HCG and HPL levels in a normal triplet gestation The asterisks represent four pregnancies with intrauterine growth retardation

The mean birth weight of 30 twin sets delivered after the 35th week of gestation amounted to 5359±883 g (±1 S D) As for the singleton pregnancies here too a significant correlation was found between the HPL level and the combined birth weight ($r=0\ 39$ $p<0\ 05$)

In the 9 pregnancies in which serum HCG could be assayed during the first trimester at least one value lay above the mean ±1 S D in 5 out of 9 cases the HCG levels exceeded the mean +2 S D During the second and third trimesters of gestation at least one HCG or HPL level exceeded the normal range (represented here by mean ±1 S D) in 28 (72%) and 29 (74%) of the 39 twin pregnancies respectively However the HPL levels were found to lie consistently outside the normal range in only about half of the cases in which at least three determinations were performed at different times during pregnancy When the data from both the HCG and the HPL assays are combined an elevated level of one or both of these placental hormones was found in 95% of the samplings This might be explained by the lack of correlation between the HCG and HPL levels In 3 out of the 4 pregnancies in which intra uterine growth retardation occurred (birth weight more than 2 S D below the mean) the value of serum HPL was abnormally low (Fig 2)

DISCUSSION

It is well established that hormones whose pattern is directly related to placental and fetal growth tend to attain higher concentrations in twin than in singleton pregnancies Probably the first to observe this trend were Jones et al (4) who reported elevated HCG levels in twin pregnancies in 1944 Later comparable observations were made for pregnancy related proteins and hormones Wald et al (6) found that in twin pregnancy maternal α fetoprotein levels were twice as high as for singletons which led these authors to warn that multiple pregnancy should be differentiated from those cases where the fetus had an open neural tube defect a condition which is likewise associated with elevated levels of α fetoprotein In a study of the urinary oestriol excretion in 50 twin pregnancies Duff & Brown (2) reported the mean oestriol levels to be 1 7 times higher than in singleton pregnancies From their data it appears that the assessment of feto placental function on the basis of maternal urinary oestriol is only reliable when both fetuses are at risk HPL levels were measured in 25 twin pregnancies by Ylikorkala (7) who found that the average concentration in the last month of pregnancy was 1 5 times higher than in singleton pregnancies and in 10 cases individual HPL values exceeded the 97 5 percentile Abnormally low HPL values were observed in only one of the two cases with severe feto placental dysfunction

Recently Gennser (3) advocated use of the HPL assay as a screening test for multiple pregnancy We too found that multiple pregnancy is associated with higher serum levels of HPL and HCG but in our opinion the fact that the diagnosis of twin gestation

cated by feto-placental dysfunction can eas missed if one relies on the HPL assay consti major drawback of the method Even though aneous determination of serum HCG and may provide a better index for the existence of ected twin pregnancy we feel that the levels hormones are too inconsistent throughout on to satisfy the criteria for a useful screening lure Nevertheless the findings indicate that confronted with elevated levels of HCG in the rimester of pregnancy as well as levels of HCG and/or HPL exceeding by 1 S D the of singleton pregnancies in the middle and rimesters the probability of a twin pregnancy l be kept in mind Finally HPL levels lying 1 S D of the mean strongly suggest the ex e of placental dysfunction

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THE CERVICAL BALLOON METHOD FOR INDUCTION OF LABOR

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act The cervical balloon (Embrey & Mollison) was induce labor in a study group of 87 patients The l group included 97 patients where induction of was performed using oxytocin drip In the study oxytocin drip was added in 34 patients The cases study and control groups were classified as e or unfavorable cervix The patients clas as unfavorable cervix showed a shorter mean on-delivery interval in the study group and a mean duration of oxytocin-drip in the cases of the where it was needed It was concluded that al balloon is a convenient method for the induc labor for its effectivity simplicity and innocuity lly in the unfavorable cervix cases

ion of labor is an obstetrical procedure hav uestionable outcome and attempts have been to introduce different methods in obstetrical ice In spite of the trend in recent years to try v drugs (1 2 3 4) or new approaches (5 6) ors were attracted by the simplicity of the using the cervical balloon described in by Embrey & Mollison (7) The purpose of this is to report our experience of using this d in a group of patients

MATERIAL AND METHODS

pectively two groups of pregnant women were d where induction of labor had to be performed for rent reasons A randomization was made by introduc he women alternately in both study and control ps Cases with ruptured membranes were excluded both groups The study group (Table I) included 87 lected patients who were distributed in two sub-ps the first 53 cases where the cervical balloon was duced and where all the patients started labor and ered without any oxytocic drug the second sub-p 34 cases where the cervical balloon was intro-ed but where the patients needed oxytocin-drip for ery Usually the cases of this second subgroup were xamined 24 hours after the catheter was introduced They were found not to be in labor although the cervix was ripe the catheter had been expelled into the vagina and oxytocin-drip was started

A 26 gauge Foley catheter was used and the 50 ml balloon was filled with 40 ml saline After exposure of the cervix with a speculum cleansing of the vagina and cervix the catheter was introduced into the cervical canal until its balloon was just beyond the internal os and the balloon was then filled No antibiotics were given preventatively The control group included 97 unselected patients where a medical induction of labor with oxytocin drip was performed

In all the cases oxytocin-drip was performed according to the following rules primipara five units of oxytocin in

Table I *Number of cases of the study group and control group*

Method	No of cases	Total
Study group		
Cervical balloon	53	87
Cervical balloon+oxytocin-drip	34	
Control group		
Oxytocin-drip	97	97

Table II *Pregnancy age at the time of induction*

Pregnancy (weeks)	Cervical balloon	Cervical balloon+ oxytocin drip	Study group (total)	Control group (oxytocin drip)
39	4	–	4	4
40	1	2	3	3
41	13	5	18	3
42	23	18	41	41
43	12	9	21	46
Total	53	34	87	97

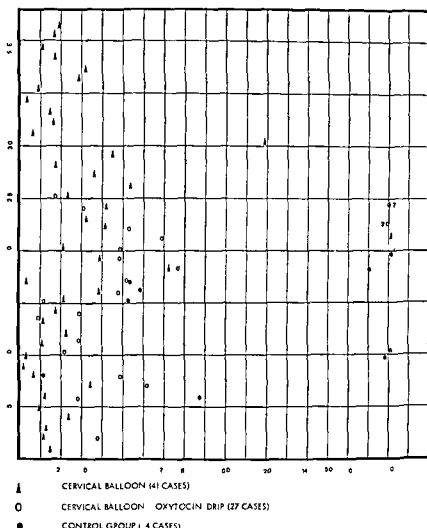


Fig 1 Comparative scattergram of induction–delivery interval (unfavorable cervix)

ml 5% glucose solution se undipara three units ertipara two units quartipara and more one unit The infusion was administered intravenously at a rate of 8–70 drops per minute The women s ages which ranged from 19 to 40 were nearly homogeneous as also was the parity from primipara to quartipara and more Pregnancy age at

Table III *State of the cervix at the time of induction*

Cervix	Cervical balloon	Cervical balloon + oxytocin drip	Group study (total)	Control group (oxytocin drip)
Favorable (ripe)	12	7	19	73
Unfavorable (unripe)	41	27	68	24
Total	53	34	87	97

the time of induction is seen in Table II The indications for induction of labor included prolonged pregnancy in those cases ending the 40th week of pregnancy (menstrual age) and were under observation to elicit real postmaturity

In cases of pre-eclampsia the induction was performed in those where there were no signs of improvement after hospitalization and treatment Other indications were diabetes missed labor uncoordinated contractions placental insufficiency and Rh incompatibility All the cases were classified either as favorable cervix or as unfavorable cervix (Table III) according to the definition of Embrey & Mollison (7) Cases with intermediate cervix were not included in this paper All the cases were head presentation except three with breech presentation one in the study group and two in the control group The weights of the newborns in both the study group and the control group ranged from 2 500 to 4 500 g

Induction–delivery interval from the beginning of the induction till the delivery

Oxytocin-drip time the time that the patient is hung with the infusion-drip running

ble IV *Induction–delivery interval and oxytocin-drip time in the study group compared with the control oup*

	Cervical balloon Mean interval induct -del	Cervical balloon+oxytocin-drip		Control group (oxytocin-drip)	
		Mean inter induct -del	Mean time (oxytocin-drip)	Mean inter induct -del	Mean time (oxytocin-drip)
	12 cases	*7 cases*		*73 cases*	
orable	27 45 h	75 14 h	3 32 h ±0 52	29 31 h	8 33 h ±0 58
nge	121 00–4 10	49 55–7 10	5 0–1 00	407 40–2 15	35 50–2 15
	41 cases	*27 cases*		*24 cases*	
favorable	28 39 h ±5 42	39 31 h ±3 41	7 44 h ±1 30	86 32 h ±20 76	15 15 h ±1 33
nge	202 35–2 70	76 15–7 00	27 00–0 50	407 20–4 30	33 30–4 30

COMMENTS

le IV shows the results of our investigation re was no substantial difference in mean induc -delivery interval between the cases in the orable cervix groups Only the possibly ificant difference in the oxytocin-drip mean between the groups with favorable cervix is th noting

the unfavorable cervix category we see that e is a clear difference between the induction–de ry interval of the study and control groups as as a marked difference when comparing the tocin drip times (Figs 1–4) The latter is ex ned by the fact that oxytocin drip as we know influence in a more decisive way when the ness of the cervix is completed By introducing cervical balloon our cases achieved cervical ness in both of the study subgroups We have no dy logical explanation why in one subgroup or developed promptly and in the other sub- up oxytocin drip was required

n one case during an attempt to introduce the vical balloon slight bleeding started placenta via was presumed and the procedure was ndoned The potential complications of the loon method are accidental rupture of the mbranes displacement of the presenting part lapse of the umbilical cord None of these was istered in our series We had no cases of infec n although three cases of puerperal pyrexia were istered in the study group and two cases in the ntrol group No antibiotic therapy was instituted her in the study group or in the control group

n our experience we have seen that by means of the cervical balloon we invariably obtain cervical ripeness and a number of cases went to delivery without any other measure Even when oxytocin drip is also required the time to reach the delivery

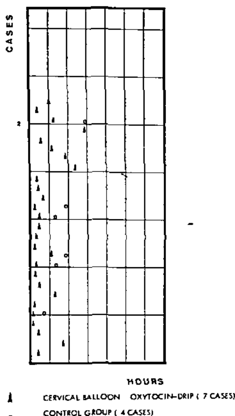


Fig 2 Comparative scattergram of oxytocin- (unfavorable cervix)

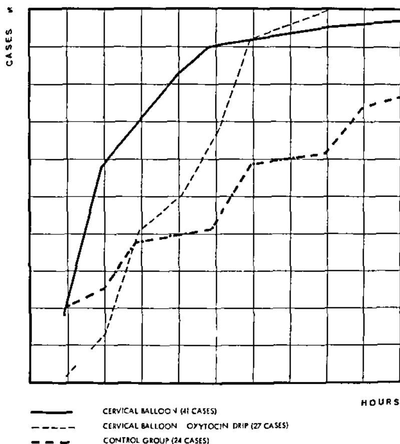


Fig 3 Cumulative curves of in duction–delivery interval (un favorable cervix)

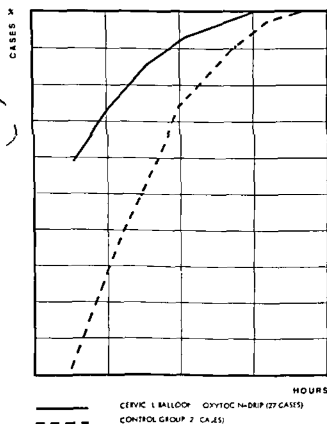


Fig 4 Cumulative curves of oxytocin-drip tin (unfavorable cervix)

orter than the time needed with oxytocin-drip ered without previous cervical balloon her point to underline is that the procedure can nued at any time and another approach assumed

rally perhaps we have the feeling that we beyond the era of the cervical bal but the experience reported here and by & Mollison (7) themselves shows that this proved to be an efficient and innocuous and ments that it would be wise to take it into Further investigations about the use of aglandins following insertion of a cervical bal are in progress

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EVALUATION OF A FETO PELVIC SCORING SYSTEM IN THE MANAGEMENT OF BREECH PRESENTATIONS

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bstract A feto-pelvic scoring system comprising mater al pelvimetric data estimated fetal weight type of reech presentation and previous obstetric history was sed in selecting patients for cesarean section or vaginal elivery A maximum score of 20 points was possible Twelve points or less indicated cesarean section During 973–1975 224 singleton breech deliveries were evaluated n 29 5 % cesarean section was performed and in 83 % of hese it could be planned in advance In 70 5 % of cases atients were allowed to deliver vaginally under contin ous electronic monitoring of the fetal heart rate There as one intrapartum death and only one early neonatal eath of a small premature child In two cases intrauterine eath had occurred already in the antepartum period The ncorrected perinatal mortality was 17 9 per 1 000 but not gnificantly different from the uncorrected perinatal mor lity of 8 0 per 1000 for all patients delivered at the anderyd s Hospital during the period 1972–1975 (12 832 irths) The corrected mortality resulting from breech resentation was 8 9 per 1000 The infants exhibited imilar and excellent 5 min Apgar scores whether de ivered vaginally or by cesarean section or matched with a andomized control series of 1 000 cephalic presentations

The relative contribution of breech presentation to erinatal morbidity and mortality is increasing as deaths from other causes decline

From an international point of view perinatal mortality in Sweden is low making the relative contribution of breech presentation to perinatal death rate even more crucial (8) The need for im proved methods in the management of breech pres entations is therefore urgent

In 1974 the present author (20) described a scor ing system based on maternal pelvimetric data estimated fetal weight type of breech presentation and previous obstetric history The advantages of this scoring system was proved to be suitable for evaluation of whether the patient before the onset of labour was a candidate for planned cesarean sec tion or vaginal delivery In a preliminary prospec tive series using this scoring system one third of the patients underwent planned cesarean section while the remaining two thirds were allowed to deliver vaginally In this series the infants exhibited similar and excellent results at the 5 min Apgar score (1) whether delivered vaginally or by cesarean section and as matched with a double control series of cephalic (occipito-anterior) presentations The present paper is an extention of the above men tioned prospective study

MATERIAL

During the period 1973–1975 224 singleton breech presen tations at the Danderyd s Hospital delivered vaginally or by cesarean section were evaluated according to the pre viously described breech index (20)

METHOD OF MANAGEMENT

X ray pelvimetry (3 4 5) was performed on all patients independent of parity when fetal weight was estimated to be well above 2 000 g Exceptions to this rule were the previously uncomplicated delivery of a large fetus as a breech presentation and obvious indications for cesarean section other than feto-pelvic disproportion

Scoring of a breech The main points considered were 1) pelvimetric data 2) estimated fetal weight 3) type of breech presentation and 4) previous obstetric history

Each variable could have a score from 0–2 points and the total maximum score was 20 points The score should exceed 12 for safe vaginal delivery Single measurements of the pelvic inlet or outlet could have a score of 1 In breech presentation sagittal and transverse pelvic inlet scores are exchangeable Zero scores excluded vaginal delivery (20)

Fetal weight was estimated by a combination of *sym physis fundus tape* measurement (comparison with a SF/ fetal weight curve) and *palpation* (20) According to the above mentioned method the mean deviation from true mean infant weight was minus 2 g In 96 randomized esti mates (true fetal weight range 1 700–4 600 g) the standard deviation was ±254 g All estimations were performed by midwives

Cesarean section was indicated when

1 One or more pelvic measurements scored zero or total score was ≤12

Table I *Feto pelvic scoring system in the management of breech presentation (20)*

Parameter	Pelvimetry and fetal weight	0	1	2	Score
Sagittal inlet		<11 5	11 5–12	>12	
Transverse inlet		<12 5	12 5–13	>13	
Interspinal dist		<10	10–10 5	>10 5	
Intertubar dist		<10	10–11	>11	
Sagittal outlet		<10 5	10 5–11	>11	
Sum of outlet		<32 5	32 5–33 5	>33 5	
Estimated fetal weight g		<1 500 >4 000	1 500–2 000 3 500–4 000	2 000–3 500	
Presentation		Double footling	Complete breech Single footling	Frank breech	
Previous vaginal deliveries		None Uncompl breech <2 kg Uncompl headpresent <3 kg Complicated delivery	Uncompl breech 2–3 kg Uncompl headpresent >3 kg	Uncompl breech >3 kg	
Soft birth canal		Unripe cervix and rigid pelvic floor	Unripe cervix or rigid pelvic floor	Ripe cervix and relaxed pelvic floor	

2 One or more pelvic measurements scored 1 and fetal weight was estimated to be above 3 500 g

3 Fetal weight was estimated to be more than 4 000 grams or less than about 1 500 g (Crush injury) (16)

4 Double footling was present (high incidence of prolapsed cord) (17)

Supervision of labour

1 Continuous FHR monitoring was mandatory The midwives were not allowed to leave the patient

2 Second stage of labour was *shortened* by intravenous oxytocin infusion because of the risk of cord compression (18) and fetal acidosis (12)

3 *Pudendal block* (or epidural) was used in all vaginal deliveries to relax the pelvic floor Perineotomy was mandatory in all nulliparae and elsewhere when needed

4 *Attendance of obstetrician pediatrician* and *anaesthetist* at the end of the second stage of labour was obligatory

5 If there were difficulties in delivering the *aftercoming head* an assistant introduced two fingers in the maternal rectum above the fetal head Pressure in a caudal direction aided the delivery of the head

In some additional cases the pelvis was too small for a breech but appropriate for a cephalic presentation Gentle external version was performed after the 35th week of gestation No anaesthesia was used but the uterus was relaxed by a terbutaline infusion Vaginal deliveries of the cephalic presentations occurred without complications

RESULTS

In 42 nulliparae and 24 multiparae cesarean sections were performed with a cesarean section rate of 29 5% (Table II) In 83% of these planned cesarean sections could be performed In two thirds of the cases the indication was fetopelvic disproportion according to the breech index In 17% and for various reasons as indicated in Table II emergency cesarean section had to be performed There were no perinatal deaths and no infant had an Apgar score of 1–3 at 5 minutes (Table III) In 10.5% assisted vaginal delivery occurred There were 68 nulliparae and 90 multiparae There was one intrapartum death resulting from failure to use fetal heart rate monitoring One early neonatal death occurred of a premature baby weighing less than 1 500 grams In two cases fetal death had occurred before the onset of labour (Table III) The uncorrected perinatal mortality for 224 breech presentations was thus 17 9 per 1000 which may be compared with an uncorrected perinatal mortality of 8 0 per 1000 for all patients delivered at the Danderyd s Hospital during the period 1972 to 1975 (12832 births) If correction is made for the antepartum deaths in the breech series the corrected perinatal mortality was 8 9 per 1 000 No infant delivered vaginally had an Apgar score of 1–3 at 5 minutes As is shown in Table III vaginal delivery of breech presentations compared favourably with cesarean sections and the results were only slightly but not significantly different from a randomized sample of 1000 cephalic presentations

DISCUSSION

Comparisons have been made on large clinical series between cephalic and breech presentations (6 9 17) and the increased complication rate in the

Table II *Indications for cesarean section (29.5 %) in breech presentation (42 nulliparae 24 multiparae)*

Indication	Number of cases	Distribution of planned and emergency cesarean sections
Planned C S		
Narrow pelvis	41	
Fetal weight >4 000 g	3	
Roomy pelvis		
Bicornuate uterus	4	
Plac praevia	2	
Pre-eclampsia	2	
I U growth retard	1	
Maternal congen muscle-dystrophia + sterilization	1	55 (83 %)
Previous cerebral palsy	1	
Emergency C S		
Roomy pelvis		
Prolapsed cord	4	
Prim. ut inertia	1	
Imminent uterine rupture	1	
Double footling	1	
No X ray		
Abruptio plac	1	
Prematurity	3	11 (17 %)

latter presentation has been stressed With the exception of a few studies (13 15 17) guidance is vague for the management of breech presentations

In order to diminish asphyxia and birth trauma in breech presentation the Zatuchni Andros breech scoring index (21) was tested at the Danderyd s Hospital However we were unable to verify the prognostic value of this index (20) The incidence of Apgar score less than 8 at one minute was lower (33 %) when the breech score was poor (0–3) than when it was high (breech score 4–8 Apgar score less than 8 at one minute in 50%) This type of breech index also has the disadvantage of not allowing planned cesarean sections to be performed

For more than a decade excellent pelvimetric X ray methods have been available for obstetric use in Sweden (3 4 5) These methods were originally designed for occipito-anterior vertex presentations In spite of this the same pelvic outlet borderline values have been used by most Swedish obstetricians for breech deliveries

It has to be realized that unmoulded heads after breech deliveries have much larger skull diameters than moulded heads of similar sized infants after vertex deliveries (20) which is one of the reasons why the pelvis must be roomier for breech than for cephalic presentations A second reason is that the shoulder width is of the same order of magnitude as the suboccipito-bregmatic diameter even if the shoulders are firmly compressed A third reason is that the crossectional diameter (fetal head plus arms) when both arms are extended over the fetal head is larger than the fronto-occipital diameter (20)

In 1971 and 1972 at the Danderyd s Hospital the risk of having an Apgar score less than 8 at one minute was nine times greater in breech presentation than for all newborn infants during the period (20) In the present paper the one minute Apgar score was omitted because it is not significantly related to cerebral palsy or mental retardation (2) For this reason the five minute Apgar score was chosen which appears to be related to neuro-pediatric handicaps Although no less than two thirds of cerebral palsies and mentally retarded cases originate from intrauterine growth retardation the contribution of traumatic breech delivery to neuro-pediatric handicaps can not be neglected any

Table III *Apgar score in singleton breech deliveries at 5 min* Breech $n=224$

Presentation method of delivery	5 min Apgar score 0	1–3	4–7	8–10	Number of cases
Breech vaginal 70 5 %	1 9 %ᵃ	0 0 %	2 5 %	95 6 %	Nulliparae $n=68$ Multiparae $n=90$
Breech Cesarean section 29 5 %	0 0 %	0 0 %	4 5 %	95.5 %	Nulliparae $n=42$ Multiparae $n=24$
Cephalic vaginal randomized sample 1974 $n=1\,000$	0 4 %	0 1 %	1 5 %	98 0 %	Nulliparae $n=397$ Multiparae $n=603$

ᵃ 2 antepartum deaths before admission to hospital

longer For this reason cesarean section for all breech presentations has been recommended (10)

However the present investigation indicates that cesarean section rate can be reduced to about 30% allowing the remaining 70% to go into spontaneous labour with minimal risk The single tragic intrapartum death could probably have been avoided had our recommendations for continuous electronic fetal heart rate monitoring been followed

No surviving infant had an Apgar score of 1–3 at five minutes The vaginal breech deliveries were as safe as those where cesarean sections were performed and the whole group of breech presentations performed nearly as well as a big randomized sample of cephalic presentations

In a recent Swedish publication (19) the main points of the present author s feto-pelvic scoring system (20) have been used prospectively and the results of the present paper have been confirmed

From a practical point of view estimation of fetal weight in the present investigation by a combination of symphysis fundus tape measurement and abdominal palpation proved to be satisfactory and better than palpation alone which has been strongly criticized (14)

Undoubtedly more precise weight estimations can be made from ultrasonic measurements of fetal abdominal circumference (7 11) However in the present case series it has not been possible to utilize onography because of lack of funds for such

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IMMEDIATE POST PARTUM INSERTION OF THE ANTIGON

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Abstract The results of intrauterine contraception using the Antigon inserted into 364 women immediately post partum are submitted The patients were followed for 24 months total number of woman months 5225 The follow up was 96 7% after 3 months 92 9% after 12 months and 89 7% after 24 months Four types of Antigon were used having surface areas from 785 to 2 740 mm² Type I and the wing model (type IV) which have the smallest surface area proved best suited The continuation rates for types I and IV after 12 and 24 months were 77 4–59 2 and 76 4–54 5 respectively These rates are on a level with those for Antigon inserted 6–8 weeks post partum It is notable that the expulsion rates (12 8 and 12 7 after 12 months) were no higher than those for Antigons inserted 6–8 weeks post partum The incidence of puerperal complications was not increased and no perforations occurred

During and immediately after a pregnancy a woman is often well motivated for contraceptional guidance but this motivation sometimes falls off soon after delivery so that she does not keep the appointment for follow up 6–12 weeks post partum (1 2) It would be a help to these women to have an intrauterine device (IUD) inserted before they leave hospital after delivery Owing to a fear that the insertion of an IUD immediately post partum might increase the risk of infection bleeding and perforation it has previously been recommended to wait until 10–12 weeks post partum (3) However a number of reports have shown that this fear is unfounded (4–10) and in a recent publication it was concluded by Rosenfield et al (11) that insertion of an IUD soon after delivery is safe and demographically the potentially most effective form of contraception The IUD most often used has been Lippes loop D generally inserted 2–4 days post partum

In the Department of Obstetrics and Gynecology section YB Rigshospitalet University of Copenhagen the Antigon has been inserted in a number of cases since 1967 just after delivery of the placenta The results are submitted below

MATERIAL AND METHOD

During the period 1967–1972 patients delivered in the Department and who wished intrauterine contraception were offered insertion of an Antigon immediately post partum 364 chose insertion at this time whereas 914 preferred waiting until 6–8 weeks after delivery Four different types of Antigon were used (Fig 1) The original model (type I) first described by Osler & Lebech (12) is kite shaped made of polyethylene measures 30×23 mm and has a surface area of 785 mm² In the bag model (type III) the original Antigon is placed in a plastic bag Its surface area is 2 740 mm² The wing model (type IV) is furnished on the inside with plastic wings connected by a cross Its surface area is 1 057 mm² In Antigon F studied by Fuchs et al (13) the frame is filled with a thin plastic membrane with horizontal slits Its surface area is 1 725 mm² The antigon has a built in magnet so that it can be checked by a galvanometer

Immediately after delivery of the placenta and after it had been ascertained that the uterine cavity was empty the Antigon was inserted manually up towards the fundus uteri which was at the same time supported from the outside Methyl ergometrine was administered intravenously (Methergin Sandoz Basle) and when the uterus had contracted the hand was cautiously withdrawn leaving the Antigon in the uterus During the insertion a light nitrous oxide anaesthesia was occasionally given

83 women had type I 133 type III 83 type IV and 67 Antigon F inserted At discharge 5–7 days post partum gynecological examination was carried out supplemented by a galvanometer test to check whether the Antigon was in situ Moreover follow up examinations were performed at 3 12 and 24 months No other form of contraception was used Tables I and II give the distribution by age and parity The insertion as well as the follow up examinations were in the hands of changing members of the obstetrical staff The follow up rate was 96 7% after 3 months 92 9% after 12 months and 89 7% after 24 months Data were analysed by the s life table method (14)

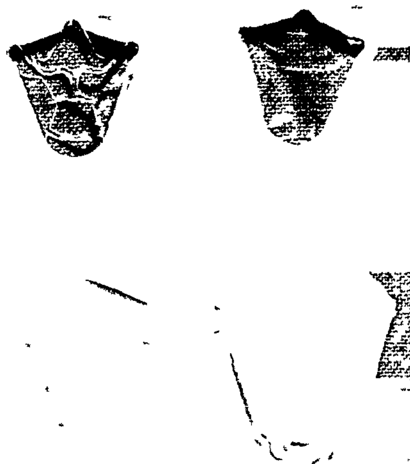


Fig 1

RESULTS

Table III presents the cumulative event rates after *12 and 24 months* for the 4 types of Antigon The 364 patients were *followed* for a total of 5225 months Re insertion of the Antigon was rarely *done* as is apparent from the continuation rates as compared with the total *event* rates

Pregnancies Five women conceived during the first years One with type I none with type III and two each with type IV and Antigon F making preg nancy rates of 1 4 0 3 1 and 3 8 respectively The differences are not significant Four conceived during the second year Two with type I one with type III none with type IV and one with Antigon F making cumulative pregnancy rates of 5 ? ? ?

Table I *Age distribution for 4 types of Antigon*

Years	Type I	Type III	Type IV	Antigon F
<18	3 (3 7%)	2 (1 5%)	0	0
18–24	27 (33 3%)	67 (50 4%)	30 (36 1%)	13 (19 4%)
25–29	22 (27 2%)	33 (24 8%)	26 (31 3%)	24 (35 8%)
30–34	16 (19 8%)	18 (13 5%)	17 (20 5%)	23 (34 3%)
>35	13 (16 1%)	13 (9 8%)	10 (12 1%)	7 (10 5%)
Total	81	133	83	67

Table II *Distribution by parity for 4 types of Antigon*

Parae	Type I	Type III	Type IV	Antigon F
I	14 (17 3%)	44 (33 1%)	30 (36 1%)	19 (28 4%)
II	23 (28 4%)	41 (30 8%)	25 (30 1%)	24 (35 8%)
III	44 (54 3%)	48 (36 1%)	28 (33 7%)	24 (35 8%)
Total	81	133	83	67

31 and 6 6 respectively The differences are not significant

Expulsions 73 Antigons were expelled during the first year including 46 during the first month post partum 15 during the second month and 2 during the third month From the 4th to the 12th month 10 Antigons were expelled Of the expelled Antigons 48 were of type III 10 each of types I and IV and 5 of the Antigon F type The corresponding expulsion rates after 12 months were 39 1 12 8 12 7 and 79 The expulsion rate for type III is significantly higher ($P<0\ 05$) than for the other types whereas no significant differences were found between types I IV and Antigon F Only 5 were expelled during the second year—1 each of types I and IV 3 of type III and no Antigon F There are no significant differences in the expulsion rates between the types during the second year

Removals 34 Antigons were removed because of bleeding/pain during the first year 4 of type I 11 of type III 6 of type IV and 13 of type Antigon F ie removal rates of 5 6 14 0 9 0 and 22 1 The removal rate for types I and IV is significantly lower ($P<0\ 05$) than for Antigon F but not for type III During the second year 21 Antigons were removed 4 of type I 9 of type III 5 of type IV and 3 of type Antigon F This makes the cumulative removal rates after 24 months 12 8 29 9 17 7 and 28 8 The rate for type I is significantly lower ($P<0\ 05$) than for type III and Antigon F but otherwise there were no significant differences between the types Only a few removals were done because of other medical or personal reasons but 22 because of planned pregnancy which gives cumulative removal rates at 24 months of 5 7 15 9 11 4 and 13 8 for types I III IV and Antigon F

Continuation rates at 12 and 24 months were 77 4 and 59 2 for type I 41 5 and 13 1 for type III 76 4 and 54 5 for type IV and 64 3 and 38 1 for Antigon F When deducting removal because of planned pregnancy the acceptability rates after 24 months are 64 9 29 0 65 9 and 51 9 respectively

Nine patients (2 5%) had either low grade temperature tenderness of the uterus and/or foul smelling discharge during the puerperium This incidence is no higher than the ordinary incidence of puerperal infection Five (1 4%) had increased vaginal bleeding There were no instances of major

Table III *Net cumulative event rates (±S E) per 100 women at 12 and 24 months for the 4 types of Antigon inserted immediately post partum*

	Type I		Type III		Type IV		Antigon F	
Months of use	12	24	12	24	12	24	12	24
Pregnancy	1 4±1 4	5 2±3 0	0	2±2 2	3 1±2 2	3 1±2 2	3 8±2 6	6 6±3 8
Expulsion	12 8±3 8	14 5±4 1	39 1±4 1	43 1±4 7	12 7±3 8	14 5±4 1	7 9±3 4	7 9±3 4
Removals								
Bleeding/pain	5 6±2 7	12 8±4 3	14 0±3 9	29 9±5 8	9 0±3 5	17 7±4 9	22 1±5 4	28 8±6 2
Other medical	2 9±2 0	4 8±2 7	4 0±2 3	6 2±3 1	0	0	0	2 9±2 9
Planning pregn	0	5 7±3 2	1 4±1 4	15 9±5 2	0	11 4±4 4	0	13 8±5 6
Personal reason	0	0	4 0±2 3	4 0±2 3	0	0	1 9±1 9	1 9±1 9
Total event rate	22 7	43 0	62 5	101 3	24 8	46 7	35 7	61 9
Continuation rate	77 4	59 2	41 5	13 1	76 4	54 5	64 3	38 1
Woman months of use	827	1437	876	1404	761	1357	6 4	1027
Number of first insertions	81		133		83		67	

Table IV *Net cumulative event rates (±S E) per 100 women at 12 and 24 months for the 4 types of Antigon*

Months of use	Type I 12	Type I 24	Type III 12	Type III 24	Type IV 12	Type IV 24	Antigon F 12	Antigon F 24
Pregnancy	3 8±1 3	9 6±2 1	2 5±1 4	2 5±1 4	5 0±1 6	5 7±1 8	3 1±1 2	3 1±1 [illegible]
Expulsion	10 3±1 9	11 4±2 1	24 8±3 7	27 6±3 9	11 3±2 3	11 9±2 4	8 9±2 0	9 6±[illegible] 1
Removals								
Bleeding/pain	8 3±1 8	12 2±2 2	11 1±2 8	19 8±3 9	15 7±2 6	24 9±3 3	14 4±2 4	26 1±3 3
Other medical	1 7±0 9	2 3±1 0	1 7±1 2	2 9±1 7	0 6±0 6	0 6±0 6	1 0±0 7	2 6±1 3
Planning pregn	3 0±1 1	7 7±1 9	4 9±2 0	17 5±3 9	0 6±0 6	7 9±[illegible] 3	3 6±1 3	12 [illegible]±[illegible] 7
Personal reason	1 7±0 9	2 3±1 0	0 8±0 8	2 1±1 5	1 7±1 0	2 4±1 [illegible]	1 0±0 7	4 1±1 7
Total event rate	28 8	45 5	45 8	72 4	34 9	53 4	32 0	57 7
Continuation rate	73 9	59 6	59 7	38 8	66 0	47 6	68 3	4[illegible] 5
Woman months of use	2 773	4 712	1 433	2 359	2 111	3 669	2 3[illegible]3	3 86[illegible]
Number of first insertions	278		161		2[illegible]7		[illegible]48	

pelvic infection or bleeding disturbances and no perforations occurred

DISCUSSION

In accordance with a number of other investigations (4–10) the present study showed that insertion of an IUD immediately or soon post partum does not involve an increased risk of puerperal infection We found increased bleeding in 5 patients (1 4%) during the puerperium Previous authors have reported be tween 2% and 24% (11) Such a wide variation is presumably due to a difficulty in assessing the ex t of the bleeding Hingorani et al (15) found no ence in hemoglobin level between two groups women with and without insertion of an IUD partum Davis (3) has recommended waiting until 10–12 weeks after delivery at which time the risk of perforation is said to be least His conclusion is based upon the data of Ratnam et al (16) Their publication shows however that the risk of perfo ration is only 0 24% at insertion within 48 hours post partum against 1 8% 4–8 weeks later and 0 42% more than 8 weeks later Moreover the ma jority of the perforations were due to an incorrect technique of insertion (16) We did not observe perforations among the 364 patients who had Antigons inserted immediately after delivery of the placenta and Banharnsupawat et al (9) found no perforations among 7 172 women who had Lippes loop inserted in most cases 2–4 days post partum Thus there is nothing to indicate that the risk of perforation is increased by inserting an IUD im mediately or soon post partum

Of the four types of Antigon I and IV had the highest continuation rates at 12 as well as at 24 months 77 4–59 2 and 76 4–54 5 against 41 5–13 for type III and 64 3–38 1 for Antigon F The bag model (type III) which has the largest surface area has a significantly higher ($P<0\ 05$) expulsion rate (39 1 after 12 and 43 1 after 24 months) than other types and a very high removal rate after 24 months (29 9) which renders this model unsuited as an IUD immediately post partum The removal rate for Antigon F because of bleeding/pain at 12 and 24 months was 22 1 and 28 8 respectively or signifi cantly higher ($P<0\ 05$) than for type I and signifi cantly higher ($P<0\ 05$) than for type IV after 12 but not after 24 months The cause of the differ ences in removal rates may be partly a difference in surface area (Antigon F has the largest surface area) and partly the fact that Antigon F was used during a later period than types I and IV Doctor and patient attitude may have changed and this may have greatly influenced the removal rates (17) Despite marked differences in surface area (785 to 2 740 mm²) there are no significant differences in the pregnancy rates between the four types of Antigon This may be due partly to the small size of the series and partly to the fact that 3–6 months elapse before full fertility has been re-established after delivery (18) Therefore any difference in the pregnancy rate will not be able to manifest itself at least during the first year

The continuation rate for types I and IV Antigons is on a level with that for Lippes loop D inserted 2–4 days post partum (9 11) but the expulsion rate (19 0 and 23 4 at 12 months) as well as the removal rate (21 1 and 23 0) are higher for Lippes loop than for the Antigon With Lippes loop however the re insertion percentage has been very high (85 and

which greatly reduces discontinuation because ... lsion After insertion of Birnberg s bow (7) and the safety filament bow (10) immediately post partum the expulsion rate has been at the same low level as in our study but the expulsion rate for Lippes loop D is higher on insertion immediately post partum than 2–4 days later (11) The difference in the expulsion rates may be due partly to differences in the technique of insertion and partly to the Antigon bow and safety filament bow adapting better to a uterus during sub-involution

The results of inserting an Antigon immediately post partum are on a level with those of insertion 6–8 weeks later This is apparent from Table IV ... shows event rates at 12 and 24 months for the four types of Antigon inserted during the same period (1967–1972) It is noteworthy that except for type III the expulsion rates are not higher for the Antigons inserted immediately post partum than for those inserted 6–8 weeks later There are also no significant differences in pregnancy or removal rates The continuation rates were a little higher for types I and IV and a little lower for Antigon F on insertion immediately post partum than 6–8 weeks later The differences are not significant

As insertion of an Antigon immediately post partum does not involve an increased risk of puerperal complications or perforations and as the results are fully up to those on insertion 6–8 weeks later insertion immediately post partum is preferable in general since this is the time at which the patient is most interested in contraception In the present study there was no difference in the results between types I and IV Antigon but type IV is preferable as previous investigations (19 20) have revealed far higher pregnancy rates for type I

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IMMUNITY TO MODIFIED SEMINAL PLASMA ANTIGENS ASSOCIATED WITH SUBFERTILITY

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Abstract The technique of counterimmunoelectrophoresis (CIE) has been used to detect precipitin reactions between sera from subfertile and fertile patients and seminal plasma antigens Freshly ejaculated seminal plasma lacked antigenicity detectable by CIE Seminal plasmas obtained as part of routine semen analyses and therefore left to stand for varying periods showed activity In a study of 60 spouse seminal plasmas which were collected in routine fashion and then incubated at 37°C antigenic activity appeared after varying periods of incubation Activity was most commonly detected after 18 hours incubation usually lasting for 6 hours or more A pool of 37 seminal plasmas (PSP) which was rendered antigenic by incubation reacted on CIE with 156 (85 7%) of 18? sera from subfertile patients and with 80 (63 0%) of 1?7 sera from fertile women In three of the positive sera the immunoglobulin fraction was recovered and found to contain the components binding with PSP antigen The PSP material was bacteriologically contaminated and on culture 7 bacterial types were isolated—pseudomonas aeruginosa proteus mirabilis bacillus subtilis non haemolytic and haemolytic diphtheroids mucoid E coli and streptococcus faecalis Pooled cell free extracts (CFE) from these bacteria reacted with 154 (84 6%) of the subfertility patients and 68 (53 5%) of the comparison subjects Use of a 3 well CIE procedure revealed the presence of some of these CFE bacterial antigens in PSP A component distinct from the bacterial antigens was observed in PSP This antigenic component is thought to represent seminal plasma antigen(s) resulting from bacterial action Its appearance is induced by contact of seminal plasma with any of the 7 bacterial types but not by incubation of sterile seminal plasma alone or in combination with CFE or bacterial protease A proportion of the bacterial antigen(s) was heat labile Those that were thermostable were removed from PSP by absorption with chicken anti ba terial antisera The absorbed PSP reacted with 58 (31 %) of the subfertile subjects and 15 (11 8%) of the fertile women The subfertile group was subdivided into primary and secondary subfertility and again according to whether conception occurred during the course of the study A difference in CIE positivity was observed in the secondary but not in the primary subfertile women Twenty two (61 1%) of the 36 secondary subfertile women who failed to conceive were CIE positive in contrast to 6 (20 7%) of the 29 women who became pregnant ($p<0.005$)

The antigenic properties of human seminal plasma as demonstrated in experimental animals are well known (7 13) Heterologous antibodies raised against various components in seminal plasma are easily detectable by commonly used techniques such as gel precipitation and passive haemagglutination with tanned erythrocytes (2 7 8)

There are very few publications on the existence of homologous antibodies to seminal plasma antigens so little is known of the immunity to seminal plasma in man There have been reports of reaginic type reactions occurring in females immediately after sexual intercourse (6 9 10) However such cases are extremely rare The antigen responsible for the anaphylactic phenomenon has been characterised as a low molecular weight non sperm coating seminal plasma protein Immune reactions to other seminal plasma components have been investigated using the techniques of gel precipitation and passive haemagglutination (8) These procedures which work well with heterologous antisera have given negative or at best doubtful results when human sera were tested The explanation for the results may be in part insensitivity of the techniques employed and in the low activity of the homologous sera

Employing the technique of counterimmunoelectrophoresis (CIE) Chen et al demonstrated the presence of antibodies to seminal plasma in the sera of infertile women and prostitutes (2 3 4 5) Carretti has also reported finding antibodies to seminal plasma components in the sera of wc

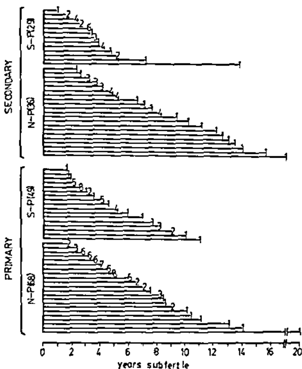


Fig 1 Composition of subfertility patients primary and secondary subdivided into those that remained non pregnant (N P) and those that subsequently became pregnant (S P) The number in each group is given in parenthesis Each line represents a common period of subfertility shared by a number of patients (given in numerals at the end of the line)

unexplained infertility using the technique of reversed passive haemolysis of cells coated with seminal plasma (1)

In our recent studies we observed that serum precipitating activity of seminal plasma under CIE appeared on standing and storage but was not present in freshly collected semen In this paper factors associated with the appearance of activity in seminal plasma are described The frequencies of reactivity to modified seminal plasma antigens have been determined in 182 subfertile women and in 127 comparison subjects

MATERIALS AND METHODS

Sera for the study were obtained from 182 patients who had no apparent organic cause for their inability to conceive and who attended the University Unit Kandang Kerbau Hospital for Women Singapore during the period 1969–1976 These patients were thoroughly investigated by clinical examination dilatation and curettage tubal insufflation and where necessary hysterosalpingogram and laparoscopic hydrotubation Full semen analyses of spouses of the patients were also performed The group of 182 patients consisted of 117 who had not been pregnant previously and who despite regular coitus over a period of 2 years or longer failed to conceive (primary subfertility) The remaining 65 had previously conceived but had failed to conceive again after attempting for a year or more (secondary subfertility) The duration of their subfertility is shown in Fig 1 Their ages ranged from 20 to 38 years with a mean of 28 6 years at the time of first consultation

Sera from the 127 fertile patients were also tested The sera comprised 82 from pregnant women 24 from women in the immediate postpartum period and 21 multipara with a parity equal or greater than 5

Reactivity of freshly obtained seminal plasma A fresh ejaculate from a healthy male was obtained Seminal plasma was prepared immediately by centrifugation at 3000 r p m for 15 min The supernatant seminal plasma was tested for reactivity with sera from 30 subfertile women by CIE These sera were previously found to be positive to pooled modified seminal plasma The conditions employed for CIE were as described before (4) except that 0 85% agarose (same source) was used and electrophoresis was continued for 75 min

Influence of incubation on spouse seminal plasmas Semen from 60 spouses was collected by masturbation into clean containers After standing at room for about 6 hours for routine analysis the semen samples were held at 4 C prior to seminal plasma recovery Each seminal plasma specimen was separately incubated at 37°C and aliquots removed at 6-hourly intervals These were tested by CIE for activity against the corresponding spouse serum and a standard positive subfertility serum (K228)

Preparation of pooled seminal plasma (PSP) and screening of study sera Seminal plasma from 37 healthy donors (comprising 34 Chinese 1 Malay and 2 Indians) were prepared after routine semen analysis had been performed The specimens were separately incubated at 37°C and activity tested by CIE using 6-hourly interval aliquots and K228 serum When a titre of activity of 1:3 or higher was reached each specimen was stored at −20°C and eventually all were pooled The sera in both subfertile and fertile study groups were tested on CIE in doubling dilutions against PSP also in doubling dilutions Five sera including K228 reacted strongly on CIE and were used as a positive sera panel

Demonstration of immunoreactivity in the CIE reactions Three of the more strongly CIE positive subfertility sera were selected and their globulin fractions salted out with a 12% concentration of sodium sulphate The fractions were dialysed against 0 01 M phosphate buffered saline pH 7 5 (PBS) and applied to N N Diethylaminoethyl cellulose columns in order to obtain the immunoglobulin fraction CIE was performed between PSP and this immunoglobulin fraction

Bacteriological studies on seminal plasma PSP was examined microscopically for the presence of bacteria Cultures were made initially on blood agar and subsequently in nutrient broth

Reactivity of study sera to bacterial cell free extract (CFE) The bacteria from PSP were cultured in nutrient

broth to provide cell free extracts which were then used to screen all the sera for antibacterial activity by CIE

Immunochemical relationship of antigens in PSP and CFE To investigate the immunochemical relation between the antigenic determinants in PSP and CFE a 3-well CIE procedure was developed involving 2 antigen wells one immediately above the other and a single antibody well 4 mm distant and punched opposite the mid point of a line joining the centres of the 2 antigen wells as illustrated in Fig 3 One hundred and fifty nine sera from subfertile women and 49 sera from comparison subjects were tested

Characterisation of antigens in seminal plasma Seminal plasmas were obtained from freshly ejaculated semen from 4 healthy donors pooled and filtered through a millipore membrane [Millex Filter Unit (0 22 μm pore size)] to exclude bacteria The pooled seminal plasmas (PS) were confirmed to be non-reactive when tested with the 5 panel sera and used as follows

1 an aliquot was kept sterile

2 equal volumes of millipore filtered CFE were mixed with equal volumes of PS and PBS (control)

3 equal volumes of pooled seminal bacteria (10% saline suspension were inoculated into equal volumes of PS and PBS (control)

All were incubated at 37°C and aliquots removed at 1 2 4 6 12 18 24 30 and 40 hours to be tested by CIE for activity against the 5 panel sera Bacterial cultures in blood agar were also taken at each stage of incubation

Each of the individual bacterial types isolated from PSP were inoculated into aliquots of an individual millipore filtered antigenically non reactive seminal plasma Activity was tested at ½ 1 1½ 2 2½ 3 4 6 10 and 18½ hours using K228 serum

Protease commercially prepared from B Subtilis (Sigma) in 20 μg amounts was incubated at 37°C in 1 ml of non reactive millipore filtered individual seminal plasma Aliquots were tested for antigenic activity at ½ hourly intervals for 3 hours and hourly for 3 hours then 4-hourly for 18 hours

Both millipore filtered PSP and CFE were heated for 10 min at 56 C 70°C 80°C and 100°C Antigenic activity was tested using 2 PSP CFE positive panel sera by CIE

To investigate the possible loss of labile antigenic component in PSP the 3 well CIE technique was used to test unheated PSP and PSP heated to 70°C

Screening of test sera for activity to heat stable components in PSP PSP was heated to 70°C for 15 min and used as antigen to screen 116 unselected subfertility sera

Bacterial-unassociated component(s) in seminal plasma Using the 3 well CIE procedure antigenic component(s) of the PSP distinct from bacterial antigens was sought in reactions with the 5 panel sera The existence of an additional component was confirmed by incubating a pooled suspension of the 7 bacterial types in a millipore filtered seminal plasma from one healthy individual and tested for activity in 3 well CIE at 6 1 18 and 24 hours against each of the 7 bacterial cell free extracts The 3 well system was also used to determine the number of antibody specificities in 4 of these sera to PSP

Removal of bacterial antigens in PSP by absorption with chicken antisera to these antigens Two male chickens were each immunised intravenously with 100 μl of a 10% pooled suspension of the 7 bacterial types and bled 1 and 2 weeks later The sera were reactive against each of the 7 bacterial antigens to a titre of 1/8 The sera were pooled and the globulin precipitated with sodium sulphate at a final concentration of 14%

PSP which was already heated to 70°C for 15 min was absorbed with the chicken globulin in a ratio of one part PSP to 8 parts globulin The mixture was kept at room temperature for 6 hours and then at 4 C overnight followed by centrifugation at 3000 r p m for 20 min to remove the precipitate The absorbed PSP was tested by CIE to determine whether bacterial antigens had been completely removed The presence of excess chicken antisera in the PSP was also checked using CFE

The absorbed PSP was then used to demonstrate the presence of the bacterial-unassociated component(s) in 3 well CIE using the 5 panel sera and CFE

Serum reactivity to absorbed PSP All the study sera were tested by CIE for activity to absorbed PSP undiluted and 1/8 diluted

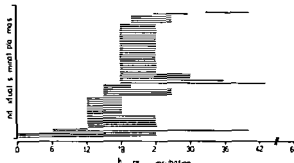


Fig 2 Incubation of spouse seminal plasmas Each line indicates the period of CIE antigenic activity of each of 60 spouse seminal plasmas under incubation at 37°C

RESULTS

In the entire group of 182 subfertile patients 78 (42 9%) eventually became pregnant during the period of study 1969–1976 These comprised 49 (41 9%) in the primary group and 29 (44 6%) in the secondary group (Fig 1)

Reactivity of freshly obtained seminal plasma No antigenic activity was demonstrated when seminal plasma from a fresh ejaculate was tested against 30 of the subfertile patients sera which were known to react with modified seminal plasma

Effects of incubation on spouse seminal plasmas Activity was observed in each of the 60 spouse seminal plasmas following varying periods of incubation at 37°C (Fig 2) Activity was detected in 4 before incubation but with the remaining and more showed reactivity at 6 12 15 18

Table I *Reactivity of sera from subfertile and comparison fertile groups to pooled seminal plasma (PSP pooled bacterial cell free extract (CFE) heated PSP and PSP absorbed with chicken antisera to bacteri antigens (absorbed PSP) tested by counterimmunoelectrophoresis (CIE)*

Study groups	No tested	Antigens used in CIE PSP positive (%)	CFE positive (%)	Heated PSP positive/total (%)	Absorbed PSP positive (%)
Subfertile					
Primary					
Non pregnant	68	55 (80 9)	56 (82 4)	21/36 (58 3)	19 (27 9)
Subsequently pregnant	49	41 (83 7)	41 (83 7)	14/35 (40 0)	11 (22 4)
Secondary					
Non pregnant	36	33 (91 7)	32 (88 9)	17/22 (77 3)	22 (61 1)
Subsequently pregnant	29	27 (93 1)	25 (86 2)	8/23 (34 8)	6 (20 7)
Total subfertile	182	156 (85 7)	154 (84 6)	60/116 (51 7)	58 (31 [illegible])
Comparison fertile	127	80 (63 0)	68 (53 5)	Not tested	15 (11 8)

hours with a peak frequency at 18 hours The last 2 to become reactive did so at 24 and 35 hours The duration of activity varied from 6 to 40 hours with 6 hours being the commonest period (40 specimens—66 7%)

Serum reactivity to PSP The titre of activity in PSP was 1/512 when tested against K228 serum The reactivity of sera from the study groups are shown in Table I One hundred and fifty six (85 7%) in the combined subfertile group and 80 (63 0%) in the comparison group were positive The difference was statistically significant (χ^2= 1 4 $p<0$ 0005) The frequency of positives in the fertile subgroups is also shown in Table I re was however no difference between the ses that subsequently achieved pregnancy and those that remained non pregnant The antibody activity of the sera was low and did not exceed 1/8

Demonstration of immunoglobulin activity in CIE reactions Precipitin bands were seen when immunoglobulin preparations of 3 CIE positive subfertility sera were tested on CIE with PSP

Bacteriological studies on seminal plasma Numerous bacteria were seen on microscopy of PSP Seven bacterial types were isolated from it They were identified as pseudomonas aeruginosa proteus mirabilis bacillus subtilis non haemolytic and haemolytic diphtheroids mucoid E coli and streptococcus faecalis

Serum reactivity to bacterial cell free extract Using K228 serum the titre of activity of the CFE was 1/32 The frequency of positives is shown in Table I with 154 (84 6%) of the subfertile group being reactive compared with 68 (53 5%) of th fertile women Again the difference between the 2 groups was significant (χ^2=35 7 $p<0$ 000 There were no differences between the subfertil sub groups (Table I) The antibody activity of th sera was again low never exceeding a titre of 1/4

Immunochemical relationship of antigens in PS and CFE Using the 3 well CIE procedure multipl bands were seen between the antibody well an each of the 2 antigen wells containing PSP or CFE Their number varied from 2 to 9 and formed com plex patterns which were difficult to interpre Some of the bands were continuous across the anti gen wells There were other bands formed with PS which were non identical with CFE and which w refer to as bacterial unassociated component(s)

Characterisation of antigens in seminal plasma No antigenic activity was detected in the sterile P even after 40 hours of incubation Sterility was con firmed by the absence of bacterial growth on cu ture

In the CFE experiment in which CFE was incu bated with PS or PBS no rise in the titre of activit was observed Bacterial growth was also absent

In the PS seeded with pooled seminal bacteri activity was detected from the first hour and pe sisted for 40 hours No antigenic activity was see in the PBS control

Inoculation of aliquots of a freshly prepare seminal plasma separately with each of 7 bacteri types resulted in appearance of antigenic activit varying from 1/2 hour to 6 hours of incubation re gardless of the type of bacterium used

Antigenic activity was not produced by incubat

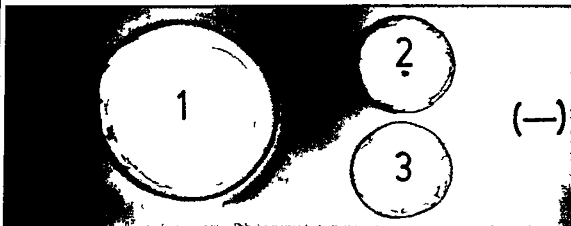


Fig 3 Immunochemical relationship of precipitin systems by 3-well CIE Test serum (1) pooled seminal plasma (*PSP*) (2) and pooled bacterial cell free extracts (*CFE*) (3) A line of partial identity is seen between *PSP* and *CFE* A line of non-identity (arrowed) is shown between *PSP* and *CFE*

ing a bacterial enzyme protease (extracted from B subtilis) with seminal plasma

When PSP was heated to 56 C its titre of activity was unchanged at 1/256 i e before and after heating However the titre fell to 1/64 after heating to 70°C It remained the same even at 100°C Similarly heating CFE to 56 C gave no change in its activity (titre 1/16) But heating to 70°C and above resulted in partial loss of activity (titre 1/4)

The loss of the heat labile component in PSP was also shown using the 3 well CIE procedure A precipitin line which was observed with unheated PSP disappeared when PSP was heated to 70°C However other precipitin lines remained indicating thermostable antigen antibody systems

Activity of test sera to heat stable components in PSP Using PSP which was heated to 70°C as antigen 116 sera from the subfertility group were screened 60 (51 7%) were positive (Table I)

Evidence for bacterial unassociated component(s) in seminal plasma The component(s) additional to bacterial antigens which was seen in earlier 3 well CIE experiments involving 159 sera from the subfertile group was again observed using 4 of the panel sera A typical result is shown in Fig 3 Three of these sera showed 2 antibody specificities the fourth had only one An example to demonstrate these specificities is given in Fig 4

Following incubation of sterile seminal plasma with the pool of 7 bacterial types the antigens produced were studied using 3 well CIE Two bands were seen but the more cathodally situated was non identical with each of the 7 bacterial cell free extracts These bands were obtained at all stages of incubation The cathodally placed band was identified as the bacterial unassociated component(s)

The same component(s) was also observed when absorbed PSP was tested on 3 well CIE There was non identity with CFE

Serum reactivity to absorbed PSP The results of serum activity to absorbed PSP are given in Table I Only 58 (31 2%) of the subfertile group reacted as compared with 15 (11 8%) of the fertile women The differences were again highly significant (χ^2= 16 7 $p<0\ 0005$) Also the total number of patients in both primary and secondary groups who were positive and subsequently became pregnant was 17 (9 3%) as compared with 41 (22 5%) who remained non pregnant However the differences within the primary group for the non pregnant and subsequently pregnant patients were not significant But in the secondary group the differences within the group were statistically significant (χ^2_s=9 1 $0\ 001>p<0\ 005$)

DISCUSSION

Previously we have reported the presence of antibodies to seminal plasma components in the sera of both infertile and fertile women using CIE (2 3 4) From the present study it is apparent that freshly ejaculated seminal plasma does not give precipitin bands on CIE The

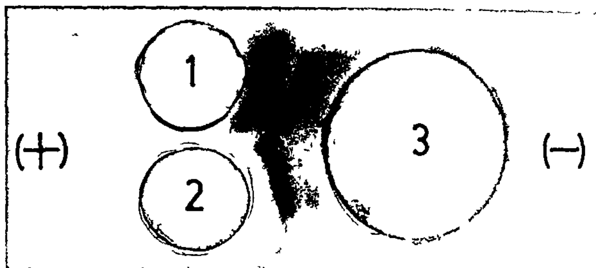


Fig 4 Number of antibody specificities by 3 well CIE between 2 sera (1 2) and pooled seminal plasma (3) A line of identity is seen between (1) and (?) indicating a common specificity A second specificity is seen with (1)

genicity appears to follow incubation with bacteria The effect can be regularly produced in any sample of seminal plasma although variation in the time of appearance and disappearance of antigenicity was observed For the purpose of obtaining antigenic preparations of seminal plasma aliquots can be sampled at different times of incubation This has enabled greater reproducibility of positive reac ions in CIE to be achieved

The role of bacterial in the appearance of seminal sma antigenicity is not understood Seven bac erial types were isolated from PSP While the sources of these bacteria were not precisely known they were presumably located around the external genetalia Incubation of seminal plasma with each of the seven types of bacteria resulted in the ap pearance of bacterial antigenicity and of antigenic ity unassociated with bacteria and therefore pre sumably associated with seminal plasma Intact bacteria were required for the production of plas ma associated antigenicity During incubation antigens of bacterial origin were released into the seminal plasma and contributed to the total anti genicity of the plasma Some of these antigenic components disappeared on heating to 70°C a fea ture which was exploited in the preparation of plasma antigenic material unassociated with bac terial antigenicity Further removal of bacterial antigenicity was achieved by absorption with chicken antisera raised against the seven bacterial types

Attention has previously been given to a possible role for bacteria in subfertility Riley & Masters (12) have cultured various bacterial types from the male partners of infertile couples Teague et al (14) found a decrease in motility and viability of sperma tozoa in the presence of E coli Quesada et al (11) reported an association of genital infection and spermagglutinating antibodies in infertile men The studies reported here lend support to the sign fi cance of bacteria in the development of seminal plasma antigenicity and hence in the induction of immunity to plasma antigens

The occurrence of immunity to modified seminal plasma antigens was investigated in 18? subfertile patients and in 127 fertile women The subfertile group had no detectable organic cause for their sub fertility Using PSP as the source of antigen 156 (85 7%) of the sera from subfertile women were positive on CIE compared with 80 (63 0%) of the fertile group Evidence that these high frequencies were in part attributable to anti bacterial im munity was obtained by the lower frequencies of positive reactions using heat treated antisera absorbed PSP Positive reactions were detected in 58 (31 2%) of the subfertile group compared with 15 (11 8%) among the fertile women

When the positive reactions were analysed in re lation to subgroups of subfertile patients it was ap parent that the higher frequency of positivity in the total group was largely due to positive reactions in 22 (61 1%) of 36 secondary non pregnant patients

The other 3 subgroups showed a lower frequency of positivity (22 7%–27 9%) which was approximately two-fold greater than that in the fertile women

The occurrence of pregnancy in primary and secondary subgroups was similar [49 (41 9%) and 29 (44 6%) respectively] suggesting that at least in the patients in this study a history of pregnancy was not of prognostic significance in terms of the probability of subsequent pregnancy Within the primary and secondary subgroups the frequency of CIE positive reactions using absorbed PSP in women who subsequently became pregnant was also similar being 11 (22 4%) of 49 and 6 (20 7%) of 29 respectively

Has a positive CIE reaction any clinical relevance? Among women in the primary subfertile group there was no relation between CIE reactivity and subsequent occurrence of pregnancy By contrast in patients in the secondary subfertile group the frequency of subsequent pregnancy was lower in the CIE positive patients Thus it does appear that CIE positivity may be of clinical significance in the evaluation of previously pregnant subfertile women Since the nature of the presumed antigen antibody system detected by CIE is unknown it is premature to speculate whether the immunity to modified seminal plasma antigen as revealed by a positive CIE reaction is causally related to reduced fertility

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INCIDENCE OF STERILITY IN WOMEN OPERATED ON IN CHILDHOOD FOR PERFORATED APPENDICITIS

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Abstract Of 80 women who had appendicectomy in child hood 78 were reviewed with reference to sterility Thirty nine of them had been operated on for acute perforated appendicitis (APA) and 39 for acute non perforated appendicitis (ANPA) There was no statistically significant difference in the incidence of sterility between the two groups In the APA group the incidence of sterility differs from that in sterility models with the same age composition It may therefore be advisable for young girls to have appendicectomy at the least indication

One of the causes of mechanical sterility is pelvic inflammation Pelvic peritonitis thus leads to steril ity in 78–94% of cases (2) Whether acute perforated appendicitis is followed by an increased inci dence of mechanical sterility remains obscure (4 6) This problem has not previously been investigated by following up cases of childhood appendicitis The present study was therefore undertaken to ele vate the incidence of infertility in females who had been operated on in childhood for acute perforated appendicitis

MATERIAL AND METHOD

The material consisted of 80 females admitted to the sur gical departments A and D Københavns Amts Sygehus in Glostrup during the period 1959–1970 In October 1975 a questionnaire was sent to all of them with questions about pregnancies unsuccessful attempts for more than one ir to conceive medical examinations because of in tility and intraperitoneal operations during the period observation A total of 78 (98%) replied and were in ided in the study

A distinction was made between infertile and fertile tients and those with unknown fertility Regarded as ertile were patients who had been involuntarily sterile more than one year Fertile were those who had been egnant after operation The patients with unknown tility had neither wanted to nor tried to conceive

The series was distributed into two groups one containing patients operated on for acute perforated appendicitis (APA) the other containing patients operated on for acute non perforated appendicitis (ANPA) The former group included 39 females ≤15 years at the time of surgery and ≥ 0 years at the time of follow-up The latter group con sisted of 39 females selected as follows following each patient operated on for APA the first consecutive patient of the same age (±1 year) operated on for ANPA entered the group In this way we obtained two groups of the same composition with regard to age and time of observation (Table I)

None of the patients had undergone intraperitoneal sur gery prior to the appendicectomy which in all cases was performed by the same method (no peritoneal lavage or drainage and closing of the wound without the use of lo cal antibiotics) In all cases the diagnosis was verified macroscopically as well as microscopically Only patients with APA were given systemic treatment with antibiotics in the form of either oxytetracycline or penicillin in combination with streptomycin

RESULTS

It appears from Table II that there were 5 sterile patients in the APA and 3 in the ANPA group The incidence of sterility was 26 and 14% respectively There was no statistically significant difference in the incidence of sterility between the groups

Table I *Mean age at the time of operation and at follow up*

Standard deviation stated in parenthesis

	Acute perforated appendicitis (APA)	Acute non-perforated appendicitis (ANPA)
Age at operation (years)	11 6 (2 6)	11.3 (2 9)
Age at follow-up (years)	23.5 (2 7)	23.5 (3 0)

Table II *Incidence of sterility in the groups acute perforated appendicitis (APA) and acute non perforated appendicitis (ANPA) calculated from the sum of sterile and fertile patients*

	Number of patients			Incidence of sterility (95% confidence limits)
	Unknown fertility	Fertile	Sterile	
APA	20	14	5	26 (9–51)
ANPA	17	19	3	14 (3–35)

(χ^2 0 4 $P<0\ 7$) The 8 infertile patients had tried to conceive for mean 25 months (S D 8 7) and at follow up their mean age was 23 6 years (S D 2 7) Two patients in either group had been subjected to investigations because of infertility In the APA group aerobic bacterial culture from the peritoneal cavity was carried out in 31 patients with a positive result in 28 (90%)

In the APA group one or more postoperative complications occurred in 13 patients (33%) Ileus developed in 1 intraperitoneal abscess in 10 and wound infection in 5 In the ANPA group post operative wound infection developed in 1 patient In each group 2 patients had undergone intra peritoneal surgery during the period of observa tion none of these patients were sterile

DISCUSSION

The effects of peritonitis can impede the migration of the ovum from the ovary to the tube and act as a potential cause of sterility The most common cause of this peritoneal factor in infertility is pelvic sepsis (2)

In addition to the peritonitis that develops when the appendix perforates postoperative complica tions are likely to increase the risk of peri tubal adhesions In our series the incidence of postopera tive complications does not differ from that found in other studies (1 5)

Powley (4) reviewed 33 patients in whom ap pendicectomy was complicated by pelvic peritonitis or the formation of a pelvic abscess They had all been under 40 years at the time of surgery The incidence of sterility was found to be high

Thompson & Lynn (6) reviewed 37 patients all of whom had been under 20 years of age when they underwent surgery for perforated appendicitis These authors did not find the incidence of sterility to be significantly increased but concluded that infertility is a potential sequel to perforated appen dicitis

In contrast to the above mentioned two studies our material consisted of children who only were ≤15 years at the time of operation and who had no previously undergone intraperitoneal surgery We could not demonstrate any statistically significant difference in the incidence of sterility between the groups APA (26%) and ANPA (14%)

In models of female sterility the incidence of in fertility in the age group 22 5 years is stated to be 3 8–6 3% In our study only the ANPA group comes within this range of infertility (cf confidence limits Table II) This would suggest an increased tendency to infertility in women who have been operated on for perforated appendicitis although this group of patients does not differ from that oper ated on for uncomplicated appendicitis

In conclusion the present investigation shows that in women who have been subjected to appen dicectomy in childhood there is no significant dif ference in the incidence of sterility between those who have been operated on for APA and those operated on for ANPA However as compared with sterility models with the same age composition the incidence of sterility in the APA group was higher than expected It may therefore be advisable for young girls to be subjected to appendicectomy whenever there is any indication to do so

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INTRA URETHRAL AND INTRA VESICAL PRESSURE IN CONTINENT WOMEN

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Abstract Two age groups of continent women were examined regarding the pressures in the urethra and the bladder using a standardized recording technique with a microtransducer catheter elaborated in 1974 by Ulmsten Asmussen The two groups of women (mean age 28 and 54 years respectively) were examined concerning their urethral pressure profile at every 100 ml bladder filling until the maximal bladder capacity had been reached The functional length of the urethra and the bladder pressure were the same for all women but the maximal urethral pressure decreased significantly with age (mean 61 5 and 39 mmHg in the two groups respectively) At increasing bladder filling only the younger group was able to respond with an increase in the maximal urethral pressure The bladder volume at which severe tenesmi occurred was significantly higher in the elderly group

Urinary stress incontinence is a frequent symptom in the female In search of the genesis of this disorder two parameters in particular have been penetrated namely the functional length of the urethra and the urethral closure pressure Changes in these are according to Lapides (10) Hodgkinson (5) and Enhorning (4) of great relevance for the pathology and treatment of stress incontinence To evaluate the findings in the incontinent female it is necessary to consider what characterizes the continent condition Therefore simultaneous urethrocystometry including the measurement of the urethral pressure profile has been performed on 22 continent women One group of women of fertile age has been compared with another group of early postmenopausal age All of them were examined with the urethral pressure profile at rest at increasing bladder volume in order to study whether the urethral pressure varied with the degree of bladder filling In addition an analysis has been made of the relationship between the urethral pressure profile and the urethral anatomy

Similar pressure studies have been made by Asmussen & Ulmsten in 1975 (1) with the same pressure recording equipment as used in this investigation Two groups of continent women with approximately the same age distribution as in this paper were examined although with a constant bladder volume The urethral pressure and the functional length of the urethra were reported to differ between the groups with a higher pressure and greater length in the younger group The greater length was probably at least partly caused by a lower bladder pressure in these women

Enhorning (4) in 1961 also reported a higher urethral pressure in younger continent women He however used somewhat less precise equipment

MATERIAL

Two groups of volunteers were examined fourteen elderly women with a mean age of 54 years (r=64–48) and 8 much younger women with a mean age of 28 years (r=36–19) The mean parity in the two groups was 1 2 (r=3–1) and 0 25 (r=1–0) respectively The criteria for participation were complete absence of incontinence symptoms or other disturbances in the urinary tract a normal gynecological status and a negative urinalysis The younger women had no symptoms from the uro-genital tract The elderly women were hospitalized for curettage because of postmenopausal bleeding In all cases the urethrocystometry was performed before the operation All women were informed of the aim of the investigation and gave their verbal consent

METHOD

Simultaneous urethrocystometry was performed with a catheter in which two microtransducers had been en

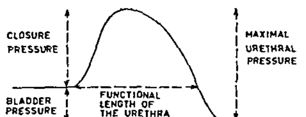


Fig 1 The curved line represents the recorded pressure from the bladder along the urethra to the external urethral meatus

closed one at the tip of the catheter and the other 60 mm proximally (Millar Instrument Inc Houston USA) For technical details concerning the recording equipment i e the catheter the amplifier and the calibration unit see the thorough discription by Ulmsten Asmussen Lindstrom 1975 (13) For the urethral pressure profile measurements the catheter was drawn through the urethra with a velocity of 2 5 mm/s by a synchronous motor During withdrawal of the catheter the end transducer continuously recorded the intra vesical pressure while the proximal transducer recorded the pressure continuously along the urethra By electronical subtraction the closure pressure was also re gistered Thus the urethral pressure the bladder pressure and the urethral closure pressure were recorded si multaneously at every moment during the examination The technique has a high precision and good reproduci bility and has been published (2)

Experimental performance

The patients were examined in the lithotomy position Residual urinary volume was measured 100 ml of 0 9% line solution at 32 C was instilled in the bladder The eter was inserted transurethrally so far into the blad that both microtransducers were located intra ically The catheter was attached to the arm of the withdrawal apparatus and three consecutive urethral pressure profiles were recorded A baby feeding catheter (outer diam 1 32 mm) was inserted transurethrally into the bladder without touching the pressure transducers and another three profiles were recorded Three urethral profiles were obtained at every 100 ml increase in bladder volume until 500 ml (the younger group) or until severe tenesmi occurred (the elderly group) At the maximal bladder volume another three urethral pressure profiles were measured without the baby feeding catheter The infusion velocity was 25 ml/min

At a bladder volume of 200 ml the urethral profile was also measured at holding urine Light and severe tenesmi were noticed as well as the absence of leakage at repeated coughs at every 100 ml increase in bladder vol ume Afterwards the patients were given urinary antiseptics prophylactically (methenaminhippurat Hiprex®)

Definitions and interpretations

Definitions according to the ICS Standard Committee 1975 (7)

Urethral pressure = The pressure within the urethra re corded in relation to the atmospheric pressure

Intra vesical pressure = The pressure within the bladder recorded in relation to the atmospheric pressure

Urethral pressure profile = Continuous recording of the intraluminal pressure throughout the entire length of the urethra

Urethral closure pressure = The intra-urethral pressure minus the bladder pressure

The functional length of the urethra = The part of the urethra where the intraluminal pressure exceeds the bladder pressure

How the parameters are measured from the records is shown in Fig 1

Three urethral pressure profiles were measured at every 100 ml bladder volume but only the third one was counted at the statistical analysis the reason being that some women had more sensitive urethras than others Involuntary movements and contractions of the pelvic floor might distort the urethral pressure profile Repeated recordings of 10 consecutive profiles under the same conditions showed that these were almost identical from the third one onwards

RESULTS

The elderly group

The mean functional length of the urethra decreased from 32 (r=44–22 5) to 28 (r=39–19) mm when the bladder volume was increased from 100 to 500 ml ($p<0.01$) Because the urethral pressure profiles were individual the differences between the functional length at 100 and 500 ml bladder volume were analyzed with Student s t test

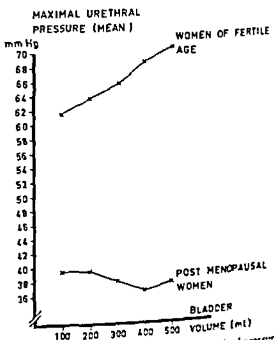


Fig 2 The change in the mean maximal urethral pressure at increasing bladder filling in the two groups



Fig 3 Comparison between a typical urethral pressure profile recorded in a woman of fertile age (A) and a post menopausal woman (B)

The mean maximal urethral pressure did not change with increasing bladder volume The mean values were approximately 39 mmHg (see Fig 2) In that part of the urethra where the pressure was highest there were pressure variations synchronous to the patient s breath and pulse The amplitudes of these pressure variations were 5–10 and 2 5 mmHg respectively As the transducer moved along the urethra during the measurement of pressure profiles these amplitudes diminished The intra individual variations in urethral maximal pressure never exceeded 5 mm when measured from repeated pressure profiles

The mean bladder pressure increased from 8 5 (r=13–5) to 12 (r=16–7 5) mmHg when the bladder volume was increased from 100 to 500 ml A slow continuous pressure increase was seen in all patients (p<0 01)

Light tenesmi occurred at a mean bladder volume of 350 ml (r=550–200) Severe tenesmi occurred at a mean bladder volume of 600 ml (r=800–400) The mean total bladder capacity was 600 ml (r=800–550)

The urethral pressure profile at holding urine was recorded in all patients at 200 ml bladder volume Only 5 patients could hold urine without contracting the abdominal muscles at the same time thereby changing the urethral pressure profile Changes in both the functional length and the maximal pressure were seen when these patients profiles at rest and at holding urine at the same bladder volume were compared

The younger group

The mean functional length of the urethra decreased from 32 5 (r=37–27) to 28 (r=31–21) mm when bladder volume was increased from 100 to 500 ml (p<0 01)

The mean maximal urethral pressure increased from 61 5 (r=82–43) to 70 5 (r=90–43) mmHg (p<0 01) (see Fig 2)

The breath and pulse synchronous pressure variations had an amplitude of 5–10 and 5–10 mmHg respectively Two patients did not increase their maximal urethral pressure at increasing bladder volume These were the only ones who did not feel severe tenesmi at 500 ml bladder volume

The mean bladder pressure increased successively in all patients from 8 5 (r=10–7 5) to 13 (r=15–10) mmHg with increasing bladder volume (p<0 01)

Light tenesmi occurred at a mean bladder volume of 190 ml (r=250–150) Severe tenesmi occurred at a mean bladder volume of 470 ml (r=600–300) The mean total bladder capacity was 500 ml (r=600–400)

No patient in this group could hold urine without simultaneously contracting the abdominal muscles

DISCUSSION

Independent of age the urethral pressure profile in the continent female was characterized by a rapid increase in pressure proximally This part of the urethra is to be regarded as an anatomical continuation of the urinary bladder (11) In the middle part of the urethra there was a pressure plateau approximately 15 mm long where the pulse and breath synchronous pressure variations were clearly seen (see Fig 3) The pressure in this part of the urethra is probably maintained by smooth and semicircular striated muscles (6 8 9 12 14) In the distal fibrous part of the urethra the pressure quickly dropped to the atmospheric pressure

The decrease in the functional length of the urethra as the bladder is filled is partly a consequence of the increasing bladder pressure Mostly there was an additional shortening of the functional length exclusively engaging the upper part of the urethra The distance from the end of the urethral pressure plateau to the only fixed point of the profile (meatus urethrae externum) seemed to be independent of bladder volume and bladder pressure Thus the additional decrease in length solely engaged the upper urethra A plausible explanation of this phenomenon is that the upper urethra sh under the weight of the filled bladder

The maximal urethral pressure in the elderly group did not alter as the bladder was filled Thus neither an increase nor a decrease in pressure was seen It has been shown (3) that the activity of the sympathetic fibers of the hypogastric nerves in creases successively during bladder filling Since the upper urethra is partly innervated by sympathe tic nerves an increase in urethral pressure would have been expected This was the case only in the younger group The largest increase in urethral pressure occurred between 300 and 500 ml bladder volume Another discrepancy between the two groups was that the urethral pressure was much higher in the younger group probably due to better vascularization This hypothesis is supported by the higher amplitude of the pulse synchronous vari ations in this group (Fig 3)

The higher bladder capacity and the later sensa tion of tenesmi in the elderly women were unex pected results They might be explained by an im paired sensibility and proprioception in the bladder and the urethra caused by diminished vasculariza tion with increasing age and a changed hormonal influence Further ageing probably brings about de generative atrophic changes in the bladder so that its capacity decreases

Light and severe tenesmi were not correlated to any changes in the parameters in the elderly group severe tenesmi were not associated with any unced increase in bladder pressure

At holding urine the bladder is displaced ventro cranially by the contraction of the muscles of the pelvic floor This is probably achieved mainly by the pelvic fascia (bladder ligaments) being stretched when the levator muscles contract Hereby the functional length of the urethra in creased uniformly The maximal urethral pressure also increased Sometimes the increase involved not only the urethral pressure plateau but also the part of the urethra proximal to this plateau Since the pressure increase affected the profile only partly and on different sites from case to case it seems likely that the levator muscles also exert a direct effect on the urethra and that this pressure increase is not accomplished by the semicircular striated muscle fibers in the urethral wall

CONCLUSION

The aim of this investigation has been to compare the pressure and pressure variations in the urethra and the bladder at increasing bladder volume at rest in two groups of continent women One group con sisted of women of fertile age and the other of women of early postmenopausal age The func tional length was the same in both groups It has further been shown that the functional length of the urethra changed with changing bladder volume There was a significant shortening of the functional length at increasing bladder filling This shortening involved only the upper part of the urethra and was partly caused by an elevated bladder pressure probably also by a slight anatomical shortening The maximal urethral pressure decreased with age In young women the urethra had the ability to react with a pressure rise on increasing bladder volume This ability was lost with age

The comparison between women of fertile and postmenopausal age showed that the functional urethral length and the bladder pressure behaved similarly at bladder filling The bladder capacity was increased and the sensation of severe tenesmi appeared later in the elderly group probably be cause of an impaired vascularization

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MANAGEMENT OF CARCINOMA IN SITU OF THE UTERINE CERVIX BY SELECTIVE LOCAL EXCISION

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Abstract Local excision of severe dysplasia or carcinoma in situ of the uterine cervix by punch biopsies was the treatment in 366 cases In 61% cervical cytology reverted to negative or slight atypia 153 patients have been followed from 1 to 7 years Failures to remove the entire lesion were discovered within the first year of follow up in all cases but 10 Complications were negligible and no patients have subsequently developed invasive cancer of the cervix Selective local excision as an alternative to other minimally traumatic techniques e g cryotherapy is discussed Although the failure rate is slightly higher with local excision an obvious advantage is the availability of all removed tissue for histopathologic diagnosis Thus the risk of overlooking microinvasive disease is reduced to a minimum

A conservative attitude towards the treatment of severe dysplasia and carcinoma in situ (CIS) of the uterine cervix prevails in the Scandinavian countries (2 8 10) The dominant procedure is therapeutic conization Recently the necessity of this procedure in all cases has been questioned It has been suggested that in selected cases local excision under colposcopic control might be an equally effective method (1) The small and inexpensive resources needed for this office procedure which is carried out without anesthesia is of potential advantage for both the patient and her physician

This is a report on the results obtained by local excision of severe dysplasia and carcinoma in situ in 366 selected patients

PROCEDURES AND MATERIALS USED

The patients in this series were selected from the general screening program for the detection and prevention of cervical cancer which has been in operation in the County of Malmöhus in Southern Sweden since 1967 Colposcopy is performed routinely in all cases of abnormal cytology When cytologic and colposcopic findings were compatible with severe dysplasia or carcinoma in situ in a large atypical transformation zone direct therapeutic conization was carried out as a rule The results of this procedure have been reported previously (2)

Patients with small areas of colposcopically abnormal epithelium in the transformation zone were treated by local excision This was performed by means of one or several punch biopsies using Schubert biopsy forceps Endocervical curettage was added when a small lesion extended into the cervical canal In a few cases when the lesion was confined entirely to the endocervix curettage was the sole procedure Bleeding following the excision was usually slight and was controlled by local application of Nelex® solution To prevent late postoperative hemorrhage and to enhance the healing process by acidification Nelex® vaginal suppositories were given every other day for a 3-week period During the same period coital abstinence was recommended Only patients with a diagnosis of severe dysplasia or CIS confirmed by histopathologic examination were included in the study

Postoperative cytologic smear control was started after 3 months When only benign cells or cells showing slight atypia were found smears were repeated every 3 months for one year and subsequently every 6–1? months In cases of evidence of persistent dysplasia or CIS therapeutic conization was usually performed However in a few cases the extension of the abnormal epithelium was still considered so limited that a second local excision was tried Those results are not included in this report

RESULTS

Total numbers of women screened and of those with a histopathologic diagnosis of severe dysplasia or CIS are listed in Table I From this table it is apparent that the patients selected for treatment with local excision are fairly evenly distributed between the different 5 year age classes The

Table I *Cytologic screening program 1967–1974 County of Malmöhus Sweden*

Year of birth	Total no screened	Total no with severe dysplasia/CIS	Total no selected for local excision	%
1913–19	11 604	82	35	43
1920–24	8 971	98	39	40
1925–29	10 460	147	89	61
1930–34	10 162	180	90	50
1935–39	10 850	127	74	58
1940–	6 587	64	39	61
Total	58 634	698	366	52

tion is the older women Obviously conservative management is less critical with increasing age In total 52% were considered candidates for the procedure

The results indicated by postoperative cytology and by time of follow up are presented in Table II The total time of follow up is given for patients whose cytology reverted to negative or to slight atypia For those with persistent or recurrent severe dysplasia or CIS the interval preceding its detection is reported In 223 patients (61%) there were no signs of residual or recurrent severe dysplasia/CIS Of these 153 have been followed for 1–7 years In a few cases one or several smears re d as benign/slight atypia were later followed by smears indicating more severe abnormalities However it is apparent that in the great majority of cases failures to remove all areas of severe intra epithelial neoplasia were detected within the first 6–12 months of follow up Only 10 patients with postoperatively negative or slightly atypical smears followed for one year or more later developed more severe neoplastic conditions Of these 8 were diagnosed during the second year of follow up and only 2 subsequently

In Table III the data have been broken down with respect to the different age-classes No distinct differences were found In fact the highest rate of residual disease occurred in the oldest and the youngest patients

Of 70 patients with a follow up of less than one year and postoperatively negative or slightly atypical cytology 16 (23%) were negative and 54 (77%) had slight atypia The latter group includes inflammatory changes and mild dysplasia (Table IV) The administrative computer program used for the screening does not permit a similar breakdown f the cases followed for one year or more Howeve the distinct impression is that early postoperati slight atypia often disappears gradually and there fore could represent an operative effect such repair No patients have developed invasive cance during the period of observation

DISCUSSION

Cytologic screening programs aimed at the detec tion and prevention of cervical cancer are wid used in many parts of the world Since the pea incidence of CIS occurs in the age group 25-3 years (4 5) and that of dysplasia even earlier screening and re screening will result in a gradu increase of the proportion of young women found have cervical intra-epithelial neoplasia This emphasizes the need for therapeutic a which inflict minimal trauma on the reproductive tract Nevertheless cure rates must be acceptabl and the risks of overlooking existing early invasi cancer or predisposing the patient for its later velopment must be negligible

With a conservative attitude regardless of technique is used willingness of the patient to un dergo regular cytologic examinations post and during several years to come is a prerequisi She must also be able to cope with the possibili that not all disease may be removed at the firs attempt In our program follow up is administere by a rather complex computer system describe previously (3) The problem of losing patients t follow up is practically non-existent

The efficacy of cervical conization in our pat population has been reported previously (7) Oth

Table II *Cervical intra epithelial neoplasia treated by local excision (overall results)*

Time after biopsy	Postoperative cytology: Negative/slight atypia		Postoperative cytology: Severe dysplasia/CIS	
<6 months		54		123
6–12 months		16		10
1–2 years	31		8	
2–3 years	30		1	
3–4 years	35	153	–	10
4–5 years	47		–	
>5 years	10		1	
Total		223		143

Table III *Cervical intra epithelial neoplasia treated by local excision (results in relation to age)*

Year of birth	Total no	Postoperative cytology: Negative/ slight atypia follow up <1 year	Negative/ slight atypia follow-up >1 year	Severe dysplasia/CIS: Total no	Occurring after 1 year
1913–1919	35	7	8	20	3
1920–1924	39	5	21	13	2
1925–1929	89	11	51	27	2
1930–1934	90	17	45	28	2
1935–1939	74	16	24	34	1
1940–	39	14	4	21	–
Total no	366	70	153	143	10

have reported on the successful use of outpatient procedures such as electrocauterization and cryosurgery (6 7 12) One potential disadvantage of these techniques is that only a limited portion of the neoplastic epithelium is removed for histopathologic examination We and others have clearly demonstrated that even in experienced hands colposcopy has limitations and will fail to pick up a certain number of early invasive lesions (2)

In this study local excision with one or multiple punch biopsies and possibly endocervical curettage is described as an alternative form of therapy in selected patients with small atypical transformation zones Even with random biopsies a certain number of patients will revert to normal cytology (9 11) In this series with colposcopically directed biopsies 61% of the cases reverted to essentially normal cytology These results are not compatible with those reported with electrocauterization or cryosurgery However the technique offers two potential advantages Firstly all tissue is made available for histopathologic examination thus reducing to a minimum the risk of overlooking microinvasive disease Secondly the depth of excision is

Table IV *Cervical intra epithelial neoplasia treated by selective local excision (distribution of negative and slightly atypical smears within first year after local excision)*

Time after biopsy	Negative	Slight atypia
6 months	10	44
6-12 months	6	10
	16	54

generally greater than can be achieved with the other two techniques

Failure to remove all neoplastic growth is in most instances detected within the first 6 months of follow up It is uncertain whether the recurrences seen later than one year after local excision represent true recurrences or progression of persisting slight atypia However with adequate follow up there is no indication that local excision as a means of controlling cervical intra epithelial neoplasia is hazardous to the patient On the contrary she will be rendered the benefit of preserved fertility and a minimal risk of complications from the treatment

ACKNOWLEDGEMENT

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CASE REPORT

SEVERE HAEMORRHAGE FROM THE NON PREGNANT UTERUS AS A RESULT OF CICATRICIAL NECROSIS AFTER CERVICAL CAESARIAN SECTION

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Abstract Two cases are reported where severe uterine haemorrhage caused by cicatricial necrosis occurred one month after cervical caesarian section The aetiology diagnosis therapy and prophylaxis are discussed and reference is made to previously reported data

Severe haemorrhage from a necrotic scar in the uterus weeks or months after caesarian section is a complication rarely reported and it is our impression that the complication as the few available reports suggest is rather unknown

Within a short interval of time two cases with this type of haemorrhage occurred in our department Treatment by hysterectomy was required

CASE REPORTS

No 1

The patient was a 23 year-old woman gravida 2 para 2 Caesarian section had been performed four years earlier in her first pregnancy and in the second pregnancy caesarian section was performed at term on the 18th January 1972 because the foetus was apparently large

At the time of the second operation the lower uterine segment was of normal appearance It was opened by transverse section and digital dilatation A live healthy boy weight 4 200 g was delivered The uterus was sutured in two layers using continuous chrome catgut no 1 while continuous plain catgut was used to close the serosa Complications of a technical nature were not encountered during surgery Lochia was normal Antibiotics were not given The patient was discharged from hospital in good health 10 days after parturition Gynaecological examination at the time of discharge from hospital showed normal conditions

The patient was re admitted as an emergency on the 17th February 197? (30 days after parturition) because of severe vaginal haemorrhage which had started two hours earlier Minor bleeding with the lochia had persisted throughout the first two weeks after surgery but in the following two weeks there had been no vaginal bleeding At admission the patient was complaining of severe constant pain at the site of the symphysis Blood pressure 100/80 pulse rate 96 Under general anaesthesia the uterus was cautiously evacuated on the suspicion that remnants of placental tissue might be present To all appearances the cavity was smooth and without remnants of tissue Still a necrotic tissue specimen measuring 1×3 cm and not resembling placental tissue was removed The haemorrhage could not be arrested and laparotomy was performed The entire cicatrix was found to be necrotic and subtotal hysterectomy according to Croback was indicated According to an estimate the overall loss of blood amounted to 3 000 ml The postoperative course was uneventful Whether or not abnormal coagulation might be in evidence was not tested

Histological examination of the uterus showed unspecific inflammatory processes in the myometrium reaction to foreign body and signs of earlier haemorrhage On examination of the tissue specimen the endometrium and the myometrium were found to be partially necrotic (Signed Per Moeller Nielsen)

No 2

The patient was a 25 year-old woman gravida 1 para 1 who was admitted at term on the suspicion of a contracted pelvis indicating induction of labour As the labour even though stimulated failed to progress satisfactorily laparotomy combined with cervical caesarian section was performed on the 28th August 1973 The lower uterine segment was found to be of normal appearance It was opened by transverse incision and digital dilatation A live healthy boy weight 4 300 g was delivered The incision into the uterus was torn during the procedure the tear extending into the parametrium to the right resulting in the formation of a minor haematoma The uterus was sutured in two layers using continuous chrome catgut no 1 Plain catgut no 0 was used for the suture of the tear The temperature was elevated at a maximum up to 38 4 C throughout the initial three postoperative days Antibiotics were not given Lochia was normal The patient was discharged from hospital in good health 10 days after surgery Gynaecological examination at the time of discharge from hospital showed normal conditions

The patient was re admitted as an emergency on the

21st September 1973 (33 days after parturition) because of the sudden onset of severe vaginal haemorrhage Minor bleeding had been an everyday occurrence after her discharge from hospital She had no pain Blood pressure 100/70 pulse rate 100 On the suspicion that remnants of placental tissue might be present in the uterus the latter was cautiously evacuated while the patient was under general anaesthesia and a few specimens of necrotic tissue were removed The cavity was found to be of smooth appearance The haemorrhage could not be arrested however and laparotomy was performed The tissue surrounding the suture in the uterus was found to be necrotic and bleeding from several vessels was noted Total hysterectomy was performed The overall loss of blood amounted to 6000 ml The postoperative course was uneventful Whether or not abnormal coagulation might be in evidence was not tested

Histological examination of tissue obtained at evacuation of the uterus showed a post partum endometrium and decidual remnants but the presence of remnants of placental tissue could not be reliably demonstrated Examination of the uterus did not reveal any true pathological post partum changes (Signed Per Moeller Nielsen)

DISCUSSION

Hansford & Weed (1) reported in 1953 for the first time that cervical caesarian section might be followed by severe vaginal haemorrhage about one month after surgery the phenomenon had been observed in two patients who were admitted by way of emergency on account of such vaginal haemorrhage caused by a necrotic cicatrix in the uterus Heys (2) described two cases of a similar nature which he had seen personally and he cited two unpublished reports on the phenomenon Reports on a further two cases of cicatricial necrosis and haemorrhage appeared in 1963 and 1974 (3 6) Stewart & Evans (7) have recently described one case where the haemorrhage apparently originated in a venous space at the corner of a thin but otherwise intact cicatrix and Manson (4) described a case where the haemorrhage originated in an aneurysmal dilatation of a venous sinus on the posterior wall of the uterus though the cicatrix remained intact

There is every reason to believe that the haemorrhage described in the present paper was caused by necrosis of the cicatrix and subsequent erosion of the vessels The necrotic tissue specimen obtained from patient no 1 was undoubtedly a fragment of the cicatrix In some of the above cited cases the necrosis may have turned into a genuine dehiscence Cicatricial necrosis may certainly not result always in severe haemorrhage occasionally it may provoke an asymptomatic dehiscence or a dehiscence which at least remains asymptomatic until a later pregnancy Pedowitz & Schwartz (5) declared on the basis of findings in a prospective study that the incidence of asymptomatic dehiscence ranged around 8 % after cervical caesarian section

It appears from the case reports that the loss of blood may be serious and accordingly it is essential to have the diagnosis established and treatment instituted without delay Treanor (8) found that the incidence of puerperal haemorrhage of a severity requiring hospitalization was 0 51 % after parturition via the vaginal route while it was only 0 27 % after delivery by caesarian section

With a view to determining whether or not a haemorrhage should be presumed to originate in a cicatrix Hansford & Weed and Heys set up the following criteria

1) that intra uterine digital palpation and cautious evacuation do not suggest other possible causes or

2) that a defect at the site of the cicatrix can be demonstrated by palpation

In the cases reported by Hansford & Weed the patients had been successfully treated with intrauterine tamponade exclusively while laparotomy had been performed in all of the other cases reported Hysterectomy is definitely the most reliable measure but other possibilities must be taken into consideration In the case reported by Keane (3) the cicatricial defect was resutured and the anterior branch of the internal iliac artery was ligated Bilateral ligation of the anterior branches or of the main internal iliac artery may also serve to bring the haemorrhage under control Even simple excision of the cicatrix and resuture may be sufficient As regards the two cases discussed in the present paper however hysterectomy was considered the only possible measure

The question to arise is whether the prevention of a cicatricial necrosis may depend on the technique used for surgery ?

It applies to both operations that continuous chrome catgut suture no 1 of the two layers of the uterine wall was used suture of the internal layer being through the entire uterine wall while suture of the external layer was rather superficial Pedowitz & Schwartz studied the various techniques used for suture but they could not give priority to one type over the others Some authors are of the opinion that continuous suture may exert a particularly traumatic effect On the other hand as a haemo-

static means it is the most valuable type of suture the perfect haemostasis thus produced is especially emphasized by Pedowitz & Schwartz The latter authors recommend the use of an inverting technique for suture thereby preventing penetration of endometrial tissue into the myometrium

Continuous catgut suture in two layers of the uterus has been used in all of the above cited cases We believe that it is the most generally used technique and reports on a few cases with the combination of haemorrhage and use of continuous suture do not justify the conclusion that such a technique is unsuitable The incision into the uterus must be made at the correct site (1) Cervical tissue is known to be incorporated into the lower uterine segment during labour and incisions at a cervical site may increase the risk of necrosis Vascularization of the cervical tissue is poor as compared with that of the lower uterine segment per se It has been pointed out by Ross & Galliford (6) that risks of incorrect incision rise parallel with the magnitude of dilatation during the preceeding labour if in progress Pedowitz & Schwartz observed that the risk of a development of cicatricial necrosis is not intensified even if patients after operation run an elevated temperature Furthermore they observed that routine administration of antibiotics after surgery was of no apparent importance for the healing of the wound

In the patients discussed in the present paper the severe haemorrhages occurred at almost identical stages after surgery namely on days 30 and 33 respectively The cicatricial necrosis observed by the above mentioned authors had been demonstrable after intervals covering from 21 to 53 days after parturition which is similar to our findings

With a view to inspecting the integrity of the scar Heys recommended the performance of hysterosalpingography of patients whenever major bleeding occurs after caesarian section

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BOOKS RECEIVED

Clinics in Obstetrics and Gynecology The Menopause vol 4 no 1 (edited by Robert B Greenblatt and John Studd) 67 pp Price per single copy £7 50 subscription price £15 00 (3 issues) W B Saunders Company Ltd England 1977

Can be recommended as a good survey with references up to 1976

I S

Guide to the Collection and Transport of Virological Specimens by C R Madeley Geneva World Health Organization 1977 40 pages Price Sw fr 10 — US$4 70 Geneva 1977

Recommended

I S

Breast Cancer Trends in research and treatment (European Organization for Research and Treatment of Cancer EORTC Monograph Series vol 2 edited by J C Heuson W H Mattheiem & M Rozencweig) 343 pp 1976

Based on the first Breast Cancer Working Conference of the European Organization for Research on Treatment of Cancer 1975 Virology immunology experimental models endocrine aspects palliative treatment curative treatment epidemiology and screening and organization of breast cancer research are dealt with Recommended to all gynecologists interested in breast cancer

I S

An Obstetric Tragedy (Editor Franco Crainz) 77 pp Price £3 50 William Heinemann London 1977

A collection of documents concerning Princess Charlotta Augusta s delivery in 1817 and her death five hours after the delivery of a stillborn son

Biochemical Methods for Monitoring Risk Pregnancies (Editor P J Keller) Vol 2 Contributions to Gynecology and Obstetrics Series 206 pp 86 figs 36 tab soft cover Price Sfr/Dm 82 — approx US$31 75 S Karger Basel 1976

A good collection of current methods which can be recommended to all departments of obstetrics and gynecology

I S

Ovulation in the Human (Editors P G Crosignani & D R Mishell) 317 pp Academic Press London New York San Francisco 1976

Proceedings from the Serono Symposium in Freiburg 1975 A good collection of basic as well as clinical research concerning ovulation

I S

Munro Kerr's Operative Obstetrics 9th ed (Editor P R Myerscough) 896 pp 310 illustr 9 colour plates Baillière Tindall London 1977

This classical book has been brought up to date and can still be recommende

I S

ANNOUNCEMENT

IIIrd Reinier de Graaf Symposium on non luteal ovarian function

The third Reinier de Graaf Symposium will be held September 4–6 1978 in Maastricht one of the oldest towns but site of the youngest Medical Faculty in the Netherlands

It will be dedicated to

a *Ovarian follicular* morphology and function from intra uterine life until the onset of puberty

b Non luteal ovarian morphology and function during the period of reproductive capacity

c Ovarian morphology and function after reproductive age

The Reinier de Graaf lecture will be delivered by Dr Hannah Peters Copenhagen

For further information please contact Prof Eylard V van Hall Department of Obstetrics and Gynaecology Leiden State University Leiden The Netherlands

Letter to the editor

Dear Sir

In the article Chorioangioma with hydramnios and intrauterine fetal death

by M Knoth et al in

Acta Obstet Gynecol Scand *55* 279 1976 there is an aspect that I found very interesting Dr Noth and associates mention that the placenta was large oedematous measuring 21×20×4 cm weighing 1150 g

Placental hypertrophy has been *reported* associated with chorioangioma both of the diffuse variety by Potter (2) and of the localised by Earn & Penner (1) and by Sen (3)

The case reported by Dr Knoth and his associates would appear to be unique in having both localised and diffuse chorioangiomas in association with placental hypertrophy

I would in particular like to ask Dr Knoth *if they* found immature oedematous villi with *small* peripheral non sinusoidal capillaries as was in the last case (3) Certainly there does not seem to be any indication of depressed placental function in these cases even though villous oedema mimicking hydatidiform mole is sometimes seen Nevertheless the perinatal mortality is high probably as indicated due to a circulatory overload on the fetal cardiovascular system The mechanism causing placental hypertrophy and proliferation of immature villi remains obscure

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2 Potter E L Pathology of the Foetus and the Infant The Year Book Publishers Chicago 1961

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Letters Å and A—see under A letters Ø and Ö—see under O

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